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Promoting Smoke-Free Homes Through Biomarker Feedback Documenting Child Exposure to Tobacco Toxins: Protocol for a Randomized Clinical Trial

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Abstract

Background: Exposure to secondhand smoke (SHS) early in life increases the risk of sudden infant death syndrome (SIDS), asthma, and respiratory illnesses. Since children's primary exposure to SHS occurs in the home, these most vulnerable members of our society are not fully protected by recent increases in the adoption of smoking bans in public spaces. Although exposure to SHS is a quickly reversible cause of excess morbidity, few low-income homes strictly enforce smoking restrictions.

Objective: This study aims to test a novel approach to motivate the adoption of home smoking restrictions and to eliminate child SHS exposure by providing parents with objective data documenting home SHS exposure and "biomarker feedback" of child ingestion of tobacco toxins, that is, objective, laboratory-based results of assays performed on child urine, documenting levels of nicotine; cotinine; and NNAL (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol), which is a metabolite of the known tobacco carcinogen NNK (4-[methylnitro-samino]-1-[3-pyridyl]-1-butanone).

Methods: From 2011 to 2013, 195 low-income, female smokers with children aged ≤10 years residing in their homes were recruited into a two-arm randomized clinical trial. Participants were assigned to one of two groups: biomarker feedback (n=98) and health education (n=97). In-home assessments were administered at baseline, week 16, and week 26. Children's home SHS exposure and nicotine, cotinine, and NNAL levels from urine samples, measured through a passive nicotine dosimeter and a surface sample of residual tobacco smoke (ie, thirdhand smoke), were collected at all three time points. Primary outcome was dosimeter-verified, self-reported complete home smoking restrictions at 6 months after randomization. Secondary outcomes included parental self-report of smoking behavior change and child urine tobacco toxin (biomarker) change.

Results: Data collection and analyses are complete, and the results are being interpreted.

Conclusions: The study protocol describes the development of a novel community-based controlled trial designed to examine the efficacy of biomarker feedback documenting home and child exposure to SHS on parental smoking behavior change.

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KEYWORDS

biomarker feedback; second hand smoke; randomized clinical trial; cessation

Introduction

Secondhand smoke (SHS) is a Class A carcinogen with no safe level of exposure. It is estimated that approximately 66% of children aged 3-11 years are exposed to SHS [1]. The human and economic costs of children's exposure to SHS are staggering and result in 400,000-1 million additional asthma attacks [2], 22,000 asthma-related hospitalizations, 1-3 million outpatient visits due to middle ear disease [2,3], and 100,000-165,000 ear tube operations each year [3,4]. Children exposed to SHS also have higher rates of behavioral and cognitive effects, including attention deficit and hyperactivity disorder [5]. Tobacco use in the home also contributes to 10,000 burn-related outpatient visits and 600 hospitalizations annually [3]. After including increased sudden infant death, exposure to SHS annually contributes to 5000 child deaths and medical costs in excess of US $10 billion [3].

Nearly 19.1 million US children younger than 18 years live in households that have a smoker, making them the most exposed age group [6]. Children are unable to avoid the main source of exposure—often, their close relatives who smoke at home. Furthermore, children have the strongest evidence of harm attributable to SHS [7]. Lower-income children suffer disproportionately from the consequences of SHS exposure, with well-documented higher rates of sudden infant death and asthma [6]. Although the roots of these disparities are complex (eg, poor housing conditions and environmental allergens), exposure to SHS is a prominent and quickly reversible cause of excess morbidity and mortality.

Two reviews detailing the literature on home SHS reduction [8-10] found mixed results. The majority of the studies combined simple self-help materials (ie, instructional pamphlets) with brief intervention (typically one session and as short as 2 minutes) delivered by a nurse or physician. A series of studies of these limited interventions [11-15] reported similar changes in home smoking bans and child's exposure in intervention as compared to non-intervention control. Compared to the uniform failure of simple self-help or brief SHS reduction interventions, more comprehensive multicomponent interventions have shown more positive effects [16-19]. Results of these trials indicate that multisession, home-based interventions involving motivational counseling might prove more effective. Although the findings for multisession counseling interventions are more promising than self-help or brief interventions, more powerful interventions are clearly needed. Only a few studies have utilized objective laboratory-based assay findings (ie, biomarkers) of children's exposure to tobacco toxins to reduce home SHS. Initial trials provided this feedback in the form of mailed brochures [20] or brief physicians phone calls to inform parents [21] about the results of biomarker testing on the child and reported null findings. Biomarker feedback seems to be more promising when combined with a more intensive counseling intervention [22,23].

The potential promise of biomarker feedback aimed at reducing home SHS exposure contrasts with a body of literature indicating its limited efficacy on smoking behavior change when used to provide a smoker with objective assay results documenting his/her own exposure to tobacco toxins [24,25]. One possible explanation for the observed discrepancy is that messages that convey risk to a child exposed to parental smoking may be more motivating than messages that convey direct risk to the individual smoker. In their reviews, McClure and Bize [24-26] speculate the other reasons why biomarker feedback to the smoker has not demonstrated a significant impact on behavior change. The first possibility is that the biomarker feedback may not have been sufficiently motivating. This could occur if the risk is perceived to be immutable (ie, a genetic risk factor) or the individual did not understand the meaning of the biomarker on which the feedback was based (ie, meaning of cotinine). Another possibility is that the individual may discount the message because he/she does not trust the source delivering the feedback. A classic line of research demonstrates that attitude change is greater when the communicator is viewed as credible, trustworthy, similar to the recipient, and not trying to change the recipients' beliefs [27,28]. Finally, elevating the perceived risk of future health consequences (the target of biomarker feedback) alone may be insufficient to bring about behavior change.

Hecht and colleagues [29] documented high levels of one of the most potent tobacco-specific carcinogens—NNAL (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol—in the urine of children exposed to SHS. This discovery raised substantial concerns within both the scientific and the public health communities, but this information has yet to be utilized to educate parents or caregivers about children's exposure to cigarette smoke in their homes.

We attended to each of these potential limitations in the design of project STARS (Start Taking Action to Restrict Smoking). STARS is a community-based, randomized trial designed to assess the efficacy of providing culturally sensitive biomarker feedback and objective data about the level of SHS in the home environment to a mother or female caregiver in order to motivate the implementation of home smoking restrictions. Feedback on their child's exposure to known carcinogens ("cancer causing chemicals") in tobacco may be more intrinsically motivating than information on other markers of SHS exposure (ie, cotinine). This information was presented by a trusted source (ie, community health workers and a counselor from the participants' local community) as part of a comprehensive intervention informed by Motivation and Problem Solving (MAPS) [30] counseling designed to empower participants to make positive changes in their own behavior and home environment. In addition, although not included in feedback to parents, we collected and analyzed dust from participants' homes to examine whether "thirdhand tobacco smoke" (THS) or the residue remaining on surfaces after a cigarette is extinguished

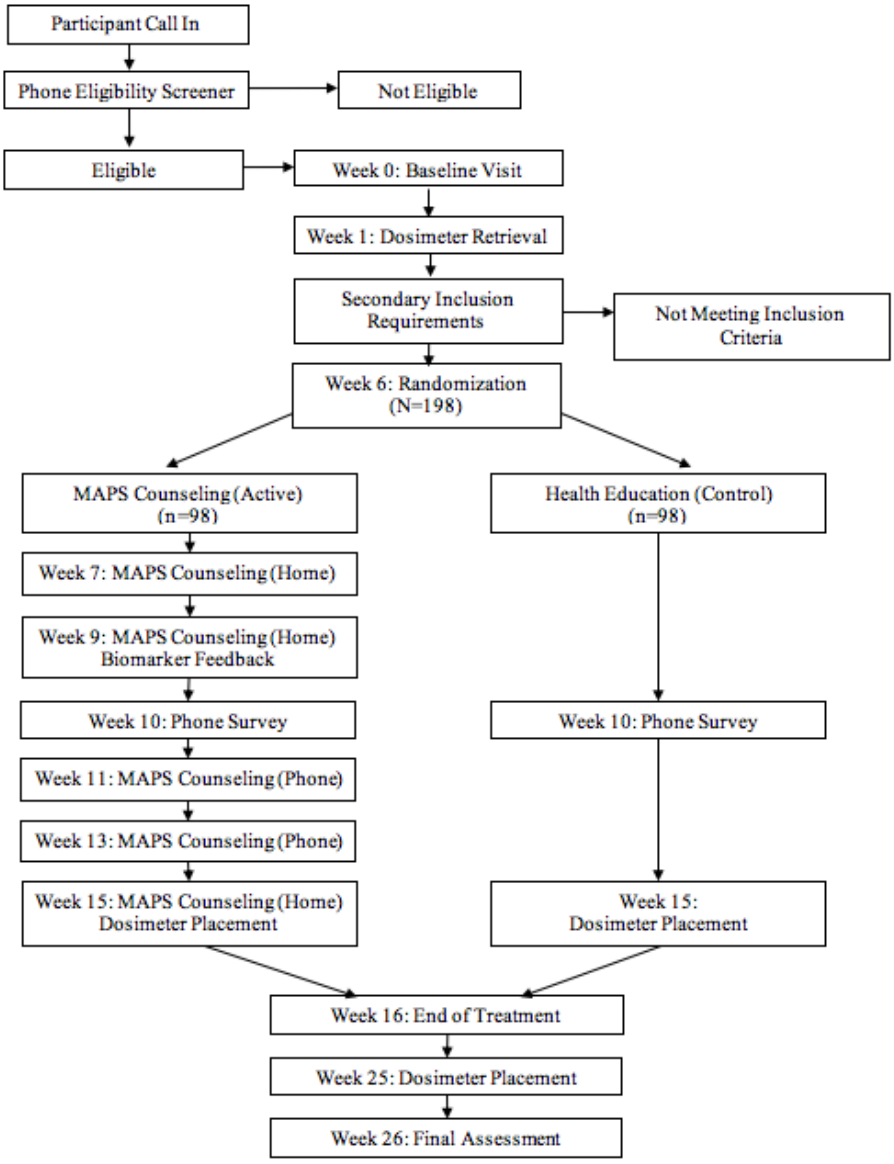
could be detected in measurable quantities. The objective of this paper is to detail our approach to building and executing this complex, community-based intervention designed to speed the translation of science from the "bench" to the "community" in order to reduce tobacco toxin exposure among children.

Methods

Study Design

Figure 1 presents an overview of the study. The primary aim of this two-group, community-based randomized trial (ClinicalTrials.gov NCT01574560) was to assess the efficacy of providing mothers with biomarker feedback documenting their child's tobacco toxin exposure on reduction of home exposure to tobacco toxins. Once eligibility was determined, participants were randomized to either the intervention arm (biomarker feedback) or the control arm (health education). At baseline, participants in both groups received a series of health education brochures designed to provide information on the dangers of SHS and THS, strategies for managing parenting stress, and tips to assist in a quit attempt. Participants randomized to the active condition were given the results of their child's urine analyses of nicotine, cotinine, and NNAL as well as the results of the home nicotine dosimeter. They also received five motivational interviewing counseling sessions, approximately 30 minutes in length, spread over 12 weeks. At each counseling session, participants were offered nicotine replacement therapy in the form of gum or lozenge (4 mg). The primary outcome was reduction in home ambient nicotine levels, objectively measured by the passive nicotine dosimeter [31] at 6 months after randomization. Secondary outcomes included child exposure to tobacco toxins measured by urinary levels cotinine, nicotine, and NNAL (a metabolite of NNK, which is a tobacco-specific carcinogen known as 4-[methylnitro-samino]-1-[3-pyridyl]-1-butanone) and a parental report of cigarettes smoked in the home and home smoking policies. Additional aims included identifying potential mediating and moderating effects of demographic variables and psychosocial and tobacco use characteristics.

Figure 1. Overview of the study procedures. MAPS: Motivation and Problem Solving.



Study Setting

The work in this trial was guided by the principles of community-based participatory research (CBPR). CBPR is an approach to research and community engagement that recognizes that the knowledge, expertise, and resources of communities often determine the success of research projects. Thus, we fully engaged our community partner in the research process [32]. Fundamental characteristics of CBPR include collaboration, empowerment, colearning, and community capacity building. An overarching key to the success of CBPR partnerships is the development of authentic partnerships. In project STARS, we partnered with a community health center serving a predominantly lower-income, African American community.

Our selected community health workers were community members chosen by our community partner agency and hired to engage the community in efforts to decrease children's exposure to tobacco toxins. As liaisons between community members and the research team, they provided cultural mediation and peer social support, advanced culturally appropriate and accessible health education and information, and increased participant access to health services when indicated [33-36]. The approach of using community health workers who are ethnically, socioeconomically, and experientially indigenous to the community has been used in prior cessation trials with success [29,37,38]. Further, evidence of the effectiveness of using community health workers in interventions targeting child health is strong. According to a 2005 Cochrane Review [39-41], community health workers are well positioned to reinforce messages and aid in the protection of children from SHS exposure.

Our community partner provided two full-time community health workers employed by the organization. The community health workers were certified health educators trained to work with individuals who may have difficulty understanding medical providers due to cultural or language barriers. Their role was to recruit, enroll, and conduct all assessment visits. The community health workers were female and indigenous to the target community, adding a source of relatedness and trust for participants. Our community health workers were also trained to interact with participants to enhance autonomy, competence, and relatedness in order to empower self-determined decision making in response to child biomarker feedback. Community health workers are thought to increase the relatedness of the intervention and positively influence message salience and comprehension, clarifying the perceived benefits of adopting home smoking bans.

The research team was located in offices in close proximity to the participant target area. In addition to the two CHWs, the research team was composed of a project coordinator, one full-time counselor from the community, one full-time research assistant, and multiple student workers, many of whom were also from the target community.

Recruitment

Participants were recruited using widespread efforts and multiple strategies throughout the Twin Cities, Minneapolis and Saint Paul, Minnesota, United States (Table 1). Targeted neighborhoods were identified, and canvassing efforts were carried out in these neighborhoods. Strategies for recruiting participants included attending local health fairs, staff informational sessions, and flyers posted throughout the community. Our primary sources of recruitment were word of mouth (snowball or respondent-driven sampling) and fliers.

The project logo was created by a local community artist and was used on promotional materials. In addition, a wide variety of community services were utilized for recruitment efforts. A partnership was also formed with a local community of churches to assist in church-based recruitment efforts.

Table 1. Community-based recruitment source.

Sources of recruitment	Method
Weekly tabloid newspaper, monthly recovery newsletter, papers, African American community	Posted advertisements
Friend, family passed along study information	Provided fliers to participants, encouraged to share
Health care	
Local clinics targeted for uninsured and underserved populations	Posted fliers, closed circuit television advertisements
Utilization of community partnership with local clinic (medical, mental, and dental services)	Posted fliers, closed circuit television advertisements, service presentation to educate staffed facilitators
Apartment buildings, grocery stores, convenience stores, nail salons, office buildings, bus stations, liquor stores, coffee shops, community hot spots	Posted fliers around the metropolitan area
Community food shelves, Salvation Army	Placed fliers in bags given to consumers
Community centers, women's resource centers, neighborhood organizations, adoption agency, participation in community events (eg, national night out, health fairs), affiliation with community organizations, Minneapolis Parks	Posted fliers, tabled at hosted events
American Indian Center, Division of Indian Work, American Indian Opportunities Industrialization Center, Minneapolis American Indian Center, Native Community Clinic	Enlisted assistance of member of the community for outreach, posted fliers
Fliers posted in elevators on University of Minnesota campus, campus dental clinic, tobacco research program hotlines	Posted fliers
Employment counselor/agency, workforce centers	Posted fliers
Treatment facilities/centers, detox, transitional housing	Posted fliers
Education	
Child care centers, day care facilities, schools	In service presentations for staff, tabled at parent events
Head start programs	Tabled at events, placed fliers in child's bag for taking home
Media	
Facebook, internet, television, Craigslist	Posted advertisements
Radio	Participated in two radio interviews and ran a public service announcement on a local channel
Church, church group	Partnered with church organization of 12 local churches, provided in-service assistance, paid organization to assist with recruitment
Case worker/manager, child protection worker, public health nurse, nursing agency, Women, Infants and Children clinics, community facilitators	In-service presentations to educate about project to share with clients, posted fliers at agencies

Participants

Prior to participant enrollment, all study procedures were approved by the Institutional Review Board. Participants called a designated study phone line to be screened for eligibility. All eligibility assessments were conducted over the phone, and initial eligibility status was determined immediately upon completion of the assessment.

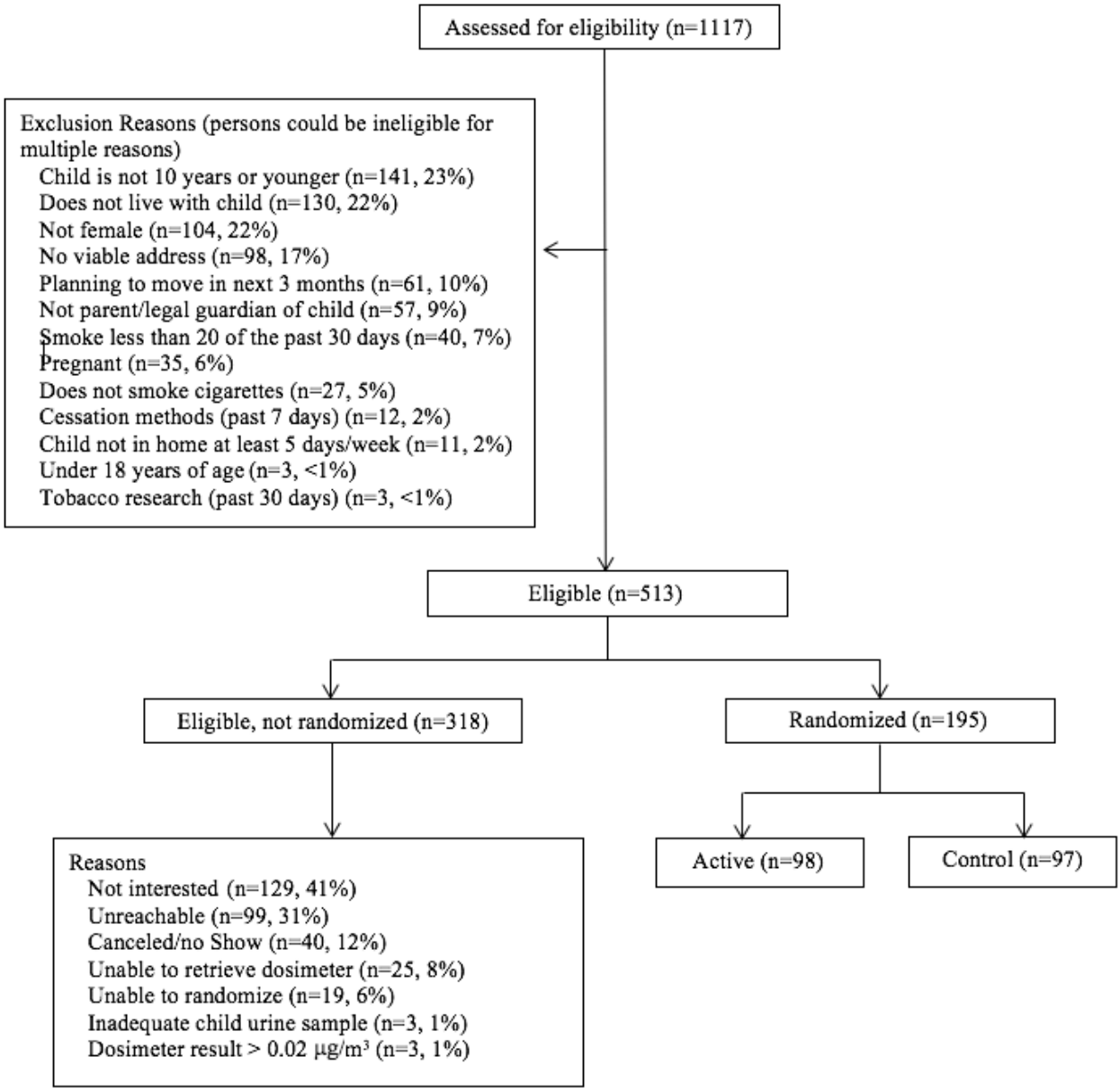
A total of 195 participants were enrolled in this study (Figure 2). Recruitment occurred over 21 months, from June 2011 to March 2013. Final follow-up assessments were completed in August 2013. Participants were randomized to either biomarker feedback (active, n=98) or health education (control, n=97) conditions. Eligible participants were female. Although we initially allowed for enrollment of male parents/guardians, we discovered that our counselor did not feel comfortable conducting home visits with a male participant. Participants were at least 18 years of age, not planning to move out of the state over the next 3 months, willing to complete three assessments in their home over a 26-week study period, and the legal guardian of a child aged ≤10 years who lives in the home on at least 5 days of the week. In order to increase the likelihood that the home environment and the child's urine assay would contain detectible tobacco toxins, participants were eligible if they endorsed smoking cigarettes on ≥20 days in the past 30 days, although they did not have to endorse smoking in the home. Participants were ineligible if they were pregnant, currently using any tobacco cessation aid (eg, counseling or NRT), homeless, living in a shelter or detox facility, living outside of a 30-mile radius of the university, or enrolled in a tobacco research study in the preceding 30-day period.

To determine positive smoking status, participants were asked to provide a urine sample at the baseline visit, which was tested using a NicAlert (Nymox Pharmaceutical Corporation, Quebec, Canada) test strip (a semiquantitative determination of cotinine levels in urine). Individuals with cotinine levels of >10 ng/mL

on the NicAlert were verified as active smokers and eligible for study participation. In addition, the child enrolled needed to provide a minimum of 17 mL of urine for sample analysis of nicotine, cotinine, and NNAL. These laboratory assay results were required to provide biomarker feedback to participants in the active condition. If a sufficient amount of urine was not collected at the baseline visit, multiple attempts were made for additional collection visits. The participant was marked ineligible for participation if a sample was not collected from the child within a 2-week window of the baseline visit.

Further, home smoking was verified using a nicotine dosimeter placed in the participant's home at the baseline visit for a total of 7 days. Upon successful retrieval of the dosimeter, a participant was considered eligible for study participation if their dosimeter value was greater than the limit of detection. The limit of detection for this study was 0.02 μg/m^3 [42].

Figure 2. Screening and enrolment of study participants.



Randomization Process

After final eligibility was determined, participants were randomized into one of two conditions: biomarker feedback or health education. A block randomization with blocks of size 4 was used to improve balance. The statistician generated the randomization numbers for the study using R [computer program] (version R 2.13.0. Austria, Vienna: R Core Development Team), which were imported into and allocated through the Research Electronic Data Capture (REDCap) database. After final eligibility was determined, the assessment staff contacted the project administrator from the participant's home to ask for the randomization assignment.

Outcome Assessment Visits

Assessment visits at baseline, week 16, and week 26 were scheduled at the convenience of the participant and were conducted by community health workers at the participant's home. Visits lasted between 60 and 90 minutes. Staff administered all surveys aloud in an interview format.

Study data were collected via an iPad using a secure, Web-based data collection instrument (REDCap) [43]. At the baseline visit, staff reviewed health education brochures with each participant in a one-time education session. The brochures provided information to participants about the risks of exposure to both SHS and THS, strategies for managing parenting stress, and tips to assist in quitting smoking. A number of additional activities took place at each assessment visit and are detailed below.

Urine Collection

Staff collected a urine sample from the youngest potty-trained child in the home. If no children in the home were potty-trained, a urine collection kit was provided to the parent for sample collection. The kit included two all-natural cotton pads, gloves, specimen bags, and an instruction sheet. Participants were instructed to wear gloves to prevent contaminating the sample with nicotine on their hands and to place a pad in the child's diaper until it was urine soaked. Participants were encouraged to collect a sample overnight, the night before the scheduled visit for heavy soaking, and collect an additional sample the day of the visit. The pad was collected during the visit and transported to our offices where the urine-soaked pad was cut into 0.5-inch wide strips using scissors and placed in a syringe. The syringe was used to extract the urine from the soaked pad. The urine was expelled into a bio specimen cup and stored in a –80°C freezer until it was sent to the laboratory for assaying.

If the identified child was potty-trained, parent assistance was requested to place a specimen commode (aka "hat") in the toilet for collection and to assist the child in sample collection. Each urine sample was analyzed for the presence of nicotine, a nicotine metabolite (cotinine), and NNAL.

Nicotine Dosimeter

At each assessment visit, staff hung a passive air nicotine dosimeter [31], which is an objective, validated method to quantify the level of ambient nicotine present in the air. The dosimeters consist of a filter treated with sodium bisulfate and contained in a 4-cm polystyrene cassette. Nicotine passively diffuses to the dosimeter and binds to the filter. The nicotine dosimeter was hung in the main activity room of each home, as well as the family car, if available. The dosimeter remained in the home and car for a minimum of 7 days for sample collection. After 7 days, staff collected and shipped the dosimeter to the University of California, Berkeley, for analysis using gas chromatography to quantify the presence of nicotine in the air.

Residual Tobacco Toxin

Surface dust sampling was collected from two locations—the home and the dashboard of the car—to assess for the presence of THS or residual nicotine and NNK remaining on surfaces after the cigarette was extinguished. A presoaked all-natural cotton wipe was used for surface dust collection. The cotton wipe was soaked with a solution consisting of 1.5 mL of 1% ascorbic acid mixed in reagent-grade water for sample preservation [44]. A 10 × 10 cm wire frame was created for precise marking of the sampling area. The moistened cotton wipe was swabbed over the 100-cm^2 area on a porous location with visible dust. This sample was taken from the same room that the nicotine dosimeter was placed in as well as another central location in the home.

Intervention Components

Participants assigned to both the active and control conditions were offered four health education brochures at the baseline assessment. Participants were provided brochures detailing information about SHS, THS (residual smoke exposure), strategies for managing parenting stress, and tips to assist in a quitting smoking attempt.

Biomarker Feedback Condition

In addition to the brochures detailed above, participants randomized to the biomarker feedback (active) condition were provided with baseline results from the child's nicotine, cotinine, and NNAL urine analysis and nicotine levels found in the home and car from the nicotine dosimeter. The information was detailed in a Participant Home Report, and information was verbally reviewed by the counselor. The target behavior in counseling, determined by the participant, was either smoking cessation or the institution of complete home smoking restrictions. Counseling was administered using MAPS counseling techniques [30]. MAPS is a unique approach, derived from a motivational interviewing framework, which utilizes motivationally based techniques to enhance commitment and intrinsic motivation for change in combination with cognitive-behavioral techniques to target self-efficacy, coping, stress, and negative effects. Participants, in collaboration with their counselor, developed a wellness plan that addresses not only smoking cessation or eliminating home smoking, but also other concerns and barriers to changing their smoking behaviors, such as parenting or relationship stress.

Counselor Training

All counseling was delivered by a female study counselor who acted as the sole counselor for all participants randomized to the active condition. The study counselor received approximately 40 hours of face-to-face MAPS counseling training, followed by additional training until performance criteria for competence and adherence to the assigned protocol were reached. The counselor participated in monthly, individual supervision to maintain performance standards. In order to monitor protocol fidelity, all counseling sessions were audiotaped, a random sample of two of the counselor's monthly sessions were coded, and detailed feedback was provided using a modified version of the Motivational Interviewing Treatment Integrity (3.1.1) [45] coding and feedback system to ensure adequate competence and adherence to the protocol.

The counselor followed a strict protocol for completion of the counseling visits and to maximize session adherence/retention. All five sessions were conducted within a 12-week window.

The first, second, and fifth sessions were conducted in the participants home, and the third and fourth sessions were conducted over the telephone. The window allowed for sessions to be scheduled every other week until the end of the counseling window. Visits were scheduled at times negotiated between the participant and the counselor. The counselor made daily attempts to reach participants to schedule or reschedule a visit. In addition, contact letters were mailed to the participant's current address and attempts were made to reach alternate contacts of persons listed by the participant, who would always know how to contact the participant.

Health Education Condition

Participants in the comparison condition received health education, which included a review of the aforementioned four health education brochures at the baseline assessment. Participants randomized to the control condition also received the baseline biomarker feedback information but at the completion of their last follow up session, to avoid influencing the study outcomes, but as a gesture of good will and gratitude for participation.

Participant Incentives

At each of the three assessment visits, participants were given a choice of receiving a gift card to either a local grocery chain or a discount department store. At baseline, participants received a US $50 gift card and an additional US $5 gift card as compensation for any cell phone usage incurred from study-based calls. Participants were also provided a small gift bag including a manicure kit, a small hair towel, a bath pillow, and a body sponge. Children were given a stuffed bear named Crystal, which was designed and marked by the American Lung Association. The bear included a short poem inscribed on the tag, which read, "Second hand smoke is not a joke! Please keep clear of smoking my dear." After completing the 16-week home visit, participants received a US $25 gift card, and a US $50 gift card was offered for completion of the 26-week visit.

Retention

To maximize retention efforts, reminder postcards were mailed to participants a week prior to all visits, and reminder phone calls were made a day before and the day of the scheduled visit. If a visit window was missed throughout study participation, the visit was marked as missed and participant contact was initiated for the next assessment visit. To minimize attrition, staff made periodic reminder calls to participants to reschedule missed visits until the window for completing appointments closed. Participants were asked to provide their home address, home and cell phone numbers, and two alternate numbers to use in the situation that they could not be reached. Participants were also sent a holiday greeting card, child and mother birthday cards, and a thank you card during their six-month participation window.

Data Management

All data management for this project utilized REDCap [46], a secure Web app for building and managing online surveys and databases. REDCap was used for data entry, data cleaning, identifying any crossovers, and conversion into proper format for data analysis and recoding using SAS [computer program] (Cary, NC: SAS Institute Inc). REDCap was also used to design and administer all assessment surveys. A REDCap tracking feature was also used to follow-up each patient and to prompt staff regarding upcoming data collection points.

Outcomes

Primary and Secondary Outcomes

The primary outcome for this study is change in home SHS exposure measured by the passive air nicotine dosimeter at 26 weeks poststudy enrollment. The specificity of the nicotine dosimeter as a marker of SHS is an appropriate marker to measure a reduction in home air nicotine. Reduction in child's cotinine and NNAL levels and parental report of smoking behavior change (ie, cessation, quit attempts, reduction, and restrictions) served as secondary outcomes. Specifically, carbon monoxide–verified, 7-day, self-reported point-prevalence abstinence assessed 6 months after study enrollment and defined as no smoking, not even a puff, for 7 consecutive days prior to the final assessment point at month 6 served as the smoking cessation measure [47]. Using a conservative approach, participants who dropped out or were lost to follow-up were considered to be smoking. Adoption of home smoking restrictions was assessed by a question modified from the Current Population Survey Tobacco Use Supplement [48]: "Which statement best describes the rules about smoking in your home?" Participants reported whether there were no bans ("Smoking is permitted anywhere"), some restriction ("Smoking is allowed in some places or at some times"), or complete restriction or ban ("No one is allowed to smoke anywhere"). Smokers were also asked to report the number of cigarettes smoked per day and the number of quit attempts in at least 24 hours since enrollment and their use of programs (eg, Helpline) or pharmacological therapy (eg, nicotine replacement therapy and other cessation medications) at weeks 8 and 26.

Treatment Effect Moderators/Mediators

In order to examine psychological mediators and moderators of the proposed intervention (exploratory aims), key factors related to important determinants of smoking behavior change were selected for each set of analyses. These included proposed moderators of effect including sociodemographic variables for parent and child, baseline smoking, and social environmental variables. Participants were asked to detail the number of days they smoked in the last 30 days, the number of cigarettes they smoked on days they smoked, use of smokeless tobacco products and other tobacco used in the last 30 days, whether they used mentholated cigarettes, the number of 24-hour quit attempts they made in the past year, the longest time period they had without smoking a cigarette, and their lifetime nicotine replacement therapy use. Other tobacco-related variables included nicotine dependence, measured using "time to first cigarette" [49] and readiness to quit smoking [50]. Alcohol use [51] (ie, number of days one drank at least one drink, number of days one drank five or more drinks) was also assessed. Social environmental variables included the number of smokers living in the home, number of adult nonsmokers living in the home, outdoor smoking options, location where most smoking occurs, and adoption of home smoking restrictions in the home and car. Child exposure to tobacco smoke was also measured (ie,

exposure to tobacco smoke in the home and outside the home in the past week). To assess any potential illnesses or health conditions that might impact the intervention or its effectiveness, parents were asked the following: "Has any health care provider ever told you that your child has any of the following illnesses: (eg, asthma, allergies, cancer, heart problems)?" Psychosocial variables included depressive symptoms (assessed using the 10-item Center for Epidemiological Studies Depression Scale [52]) and stress (measured using the 4-item Perceived Stress Scale [53]). Social influence was measured by asking how many of the participant's five closest friends smoked cigarettes [54], and social support was measured via the Partner Interaction Questionnaire (Short-Form) [55]. Participants' view of their social standing in the community and the nation was assessed using the MacArthur Scale of Subjective Social Status [56].

Key mediators are important behaviors, attitudes, and beliefs related to both the proposed intervention and the outcomes. Optimism bias was assessed using a modified version of the Smoking Hazards Scale [57], a 12-item questionnaire with four scales designed to assess perceptions of obvious and subtle health risks due to smoking and other health behaviors. We modified the existing measure to assess perceptions regarding the child's exposure to SHS. The Passive Smoking Outcomes Expectations Scale [17] was used to assess parents' expectations of the outcomes that may result from their children's exposure to SHS. Intrinsic motivation was assessed with the Treatment Self-Regulation Questionnaire [58-60]. We used this tool to measure intrinsic and extrinsic motivation in order to adopt home smoking bans and quit smoking. Smoking abstinence self-efficacy was assessed using the 12-item Smoking Self-Efficacy Questionnaire, and self-efficacy to engage in behaviors to decrease child SHS exposure (eg, adopt home smoking bans) was measured using the Passive Smoking Outcomes Expectations scale [17]. To assess whether receipt of biomarker feedback was associated with changes in motivation and confidence to quit smoking/adopt home smoking bans, participants were asked "How motivated are you to quit smoking/adopt bans?" and "How confident are you in your ability to quit smoking/adopt bans?" In order to assess message salience and comprehension, at the conclusion of each of the three counseling sessions, participants were asked a series of five questions to assess their comprehension and ability to relate to the material presented during that session. Finally, social support for both cessation and adopting home smoking bans was measured using an abbreviated version of the Partner Interaction Questionnaire [61], consisting of six items designed to assess both positive and negative support behaviors [62].

Sample Size and Power Considerations

The sample size was chosen to ensure adequate power in order to examine the efficacy of tobacco-specific biomarker feedback in terms of the difference of SHS home exposure (primary outcome) between the two treatment groups at week 26. The power calculation was based on two-sided, two-sample *t* test assuming a type I error of 0.05. A total sample size of 180 (90 per treatment group) was determined to achieve 85% power in order to detect an expected difference (between 1.15 [SD 1.58] $\mu g/m^3$ for the biomarker feedback group and 1.89 [SD 1.68] $\mu g/m^3$ for the health education group) in air nicotine levels measured by dosimeters, which was derived from the assumed adoption rates of home smoking bans of the two treatment groups (55% vs 25%).

Statistical Analysis

Primary Analyses

For the continuous end points such as reduction (ie, change score) in SHS home exposure (primary outcome), child urinary cotinine levels (secondary outcome), and parental self-report amount of smoking, the primary analysis will be the two-sided *t* tests for the measurements at week 26. In case the distribution of nicotine or cotinine level shows nonnormality, the logarithm transformation on the biomarkers or nonparametric Wilcoxon rank sum test will be applied. Categorical variables such as the adoption of home smoking restriction policies and parental quitting behaviors will be analyzed using a Chi-square test (or the Fisher exact test if there are cells with a frequency ≤ 5).

Secondary Analyses

Supportive analyses will include multivariable regressions accounting for the effect of relevant baseline sociodemographic, tobacco-related (eg, cigarettes smoked per day), and psychosocial variables (eg, depression), especially if significant effects on the outcomes or imbalance between the study groups are discovered. To utilize the repeated measures data more efficiently, we will also use linear mixed models for the continuous endpoints and the generalized linear mixed models for the binary endpoints. All regression models will include treatment, time, and possibly interactions between treatment and time, after adjusting for other aforementioned covariates. The model-based and empirical estimates of the endpoints for both treatment arms at each of the three time points will be generated and displayed with appropriate tabular and graphical methods.

Missing Data Analyses

We will use the intent-to-treat method to include all subjects who were randomized in the final data analysis. For subjects with missing data at week 26, a zero change score will be imputed. As a supplementary analysis, we will also use the completers-only method to analyze variables with missing values.

Moderator and Mediator Analyses

Potential treatment effect moderators will be tested by including their main effect and interaction with the treatment group in multivariable regressions. For the analysis of potential mediators, we will employ the four-step logistical process of testing mediational effects developed by Baron and Kenny [63] and others and summarized by Frazier et al [64]. We will also use structural equation modeling techniques to examine the full pattern of predicted mediational pathways. We propose to develop a series of three models to examine how the proposed interventions influence the process of smoking behavior change. The first step in the process is to examine if there is any relationship between the proposed intervention and behavioral determinants as defined by our theoretical model. This step will involve the development of models, with each

key behavioral determinant being the dependent variable (Model A). The next model will examine how changes in behavioral determinants are related to interim outcomes, that is, week 16 outcomes (Model B). The final model will examine how changes in behavioral determinants at the interim (16 weeks) evaluation are related to the outcomes at the final evaluation (26 weeks; Model C).

Results

Ethical approval was received from the University of Minnesota's Human Research Protection program (Institutional Review Board code number: 0909M72004). Enrollment and analyses for the study are complete, and data interpretation is underway.

Discussion

Project STARS is one of the first community-based trials to use culturally sensitive biomarker feedback given to the smoking parent or caregiver on their child's exposure to tobacco toxins. The goal of the study was to reduce SHS exposure in the home, and the intervention was designed to target the smoking mother or female guardian of the child. However, there could be multiple smokers in the home (ie, spouse, partner, or grandparent). Participants were counseled on how to discuss SHS and negotiate home smoking restrictions with others living in the home or visiting the home, but family and social dynamics often complicated the execution of the rules. Further, the majority of our participants lived in areas of high social and economic disadvantage and had competing priorities and additional stressors in their lives that made smoking restrictions difficult. Their desire to create a smoke-free environment for their children was hindered by their physical environment and their responsibilities to care for their children. For example, it was not always plausible to smoke outside of their apartment because the neighborhood was not safe or they could not leave their child alone in the building without supervision. A series of focus groups with smoking mothers in disadvantaged areas found that the need to protect their child's health was clearly set against competing demands, such as the need to relax and maintain social relationships and the need to be actively present to care for the child and prevent them from harming themselves [65].

Another potential complication was the amount of time the child spent outside of the home. To be considered eligible, the child had to be present in the home 5 days a week, but the number of hours spent in the home was not specified. The child may have spent time in other homes where smoking occurred. Further, children may have ridden in cars, other than their mother's car, where a driver or passenger was smoking. Although this was assessed in follow-up surveys, it is difficult to obtain an accurate picture of the amount of time the child spent with other smokers. This will be important to keep in mind as we analyze the data from the nicotine badge and the child's urine assays, as the two sources of measurements may not correlate with each other.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the National Center on Minority Health and Health Disparities.
[PDF File (Adobe PDF File), 301 KB - resprot_v8i10e12654_app1.pdf]

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Abbreviations

CBPR: Community-Based Participatory Research
MAPS: Motivation and Problem Solving
REDCap: Research Electronic Data Capture
SHS: secondhand smoke
STARS: Start Taking Action to Restrict Smoking
THS: thirdhand smoke

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Protocol

Evaluation of a Custom-Developed Computer Game to Improve Executive Functioning in 4- to 6-Year-Old Children Exposed to Alcohol in Utero: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Fetal alcohol spectrum disorder (FASD) is one of the most common causes of preventable intellectual disability, and the key associated deficits are in executive function (EF). Aspects of EF can be improved using cognitive training interventions. The highest prevalence of FASD globally (at a rate of 135.1 per 1000) has been found in a South African population in the Western Cape province. There is a shortage of specialized health service personnel, and there are limited remedial services. Computer-based cognitive training, if age and culturally appropriate, could be an effective way to provide the interventions with minimal need for skilled personnel and other resources. The Foundation for Alcohol Related Research has developed such a program for the South African context.

Objective: This protocol aimed to evaluate whether it is feasible to use computerized cognitive training in a resource-poor context to improve cognitive function in children exposed to alcohol in utero.

Methods: We are conducting a randomized controlled trial in the Saldanha Bay Municipal area, evaluating a custom-developed cognitive training program to improve the cognitive function of children aged between 4 and 6 years who were exposed to alcohol in the prenatal stage. Participants will be recruited from local Early Childhood Development centers. Community workers will interview biological mothers to identify alcohol-exposed pregnancies. Alcohol-exposed children will be randomized into an intervention or a control group of 40 participants each using block randomization. A group of 40 children not exposed to alcohol will be included in a normative group using individual randomization. The intervention group will play the game for 6 months (40 sessions). Normative and control groups will receive no intervention. Neurodevelopmental assessments will be done at baseline and upon completion of the study with all participants.

Results: The intervention has started, and all baseline assessments have been done at the time of submission.

Conclusions: This study will provide insight into whether computerized cognitive training is viable and effective in the South African context. It has the potential to provide a means of intervention globally and in other resource-poor context and expand

the knowledge base regarding executive functioning and FASD. This paper presents the research protocol and intervention design of the study.

Trial Registration: ISRCTN Registry ISRCTN17244156; http://www.isrctn.com/ISRCTN17244156.

International Registered Report Identifier (IRRID): DERR1-10.2196/14489

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KEYWORDS

protocol; fetal alcohol spectrum disorders; FASD; cognitive dysfunction/prevention and control; executive function; experimental games; brain/drug effects; child development

Introduction

Background

Consuming alcohol during pregnancy is one of the most common causes of preventable intellectual disability [1]. The teratogenic effects of alcohol can lead to a range of physical and intellectual difficulties and disabilities, grouped together under the term fetal alcohol spectrum disorders (FASDs) [2]. To date, the highest prevalence of FASD globally has been found in selected communities in South Africa, with a prevalence rate of 135.1 per 1000 in a particular population in the Western Cape province and 119.4 per 1000 in the Northern Cape provinces [3-5].

Deficits in both elementary and higher order intellectual functioning have been found in FASD. It has been established that some of the key deficits in children are in the domains of attention, information processing, and executive function (EF) [6]. The deficits found in attention are associated specifically with encoding (temporarily holding information in memory to perform mental operations on it) and shifting (flexibly moving attention between different stimulus dimensions), along with deficits in executive control [7,8]. The EF that is found to be affected includes inhibitory control, cognitive planning, and working memory [7,9].

Cognitive Training

Dysfunctions in EF can have serious consequences and have been associated with poor school readiness, addiction, conduct disorder, and lower educational outcomes [10]. Owing to the deficits in EF, individuals with FASD struggle with integrating knowledge and basic cognitive processes required for complex tasks [7]. Intervention in these areas is crucial as deficits have an impact on social functioning, adaptive functioning, and the ability to live independently. It has been shown that aspects of EF can be improved using training and practice [11]. Interventions include physical activities such as martial arts and yoga, improved school curricula, and computerized cognitive training [11,12]. Cognitive training has shown to have an impact on task performance and on fluid intelligence (Gf) tests [13-15]. Training on specific cognitive tasks induces neuroplasticity, and although the specific mechanisms are still unclear, it is generally accepted that training impacts synaptogenesis and neurogenesis [16]. Evidence that these mechanisms can improve the brain's functioning has been found in populations including individuals with traumatic brain injury [17], individuals with unspecified mild or moderate mental retardation [18], and children with FASD between the ages of 6 and 15 years [19].

The impact of the improvement in specific functions is not yet clear, and results of studies examining this have been mixed [14,20]. The key question in this regard is whether training can have an impact on fluid intelligence and therefore global intellectual functioning. Although the idea that training can impact Gf has been challenged [15], there is some evidence to support it [21-23]. The sequela of the cognitive deficits associated with prenatal alcohol exposure (PAE) arguably have the most severe impact on life outcomes [24,25]. Early diagnosis and intervention can improve expected life outcomes [26]. Yet, in South Africa, an acknowledged lack of specialized health services and personnel [27] means that few affected children will be diagnosed early, and those that are diagnosed will likely not have access to any remedial programs or intervention.

Cognitive Training in Resource Poor Contexts

Cognitive training interventions do not translate easily into a resource-poor context, and even physical activities such as martial arts and yoga require a trained interventionist. Computer-based cognitive training, if age and culturally appropriate, could be an effective way to provide the interventions with minimal need for skilled personnel and other resources. Unfortunately, existing games such as cognitive carnival or Caribbean quest [19] and other brain training games require a level of computer literacy not routinely found among low-socioeconomic status (SES) children owing to low levels of exposure to computers [12]. The game, Caribbean Quest, for example, requires children to use a keyboard and mouse. These skills would have to be taught to the children, and in some settings may serve as a confounder when measuring game performance. Participants in the Caribbean Quest study also had one-on-one sessions where they were taught meta-cognitive skills. Although this proved to be effective, in a resource-poor context, this would not be viable on a large scale [19].

In comparison with the Canadian study [9], children diagnosed with FASD in South Africa live in social environments different from those in Canada and the available resources are scarce. Participants in the cited cognitive training studies were either already receiving other rehabilitation services [17,18] or the intervention went further than only providing the cognitive training game [19]. Therefore, the question remains whether computerized cognitive training can be adapted for a resource-poor context and whether it will still have an impact.

One of the main differences between the 2 contexts is the access to personal computers and laptops. To develop games for personal computers and laptops will therefore likely exclude many participants in low-SES communities. The required skills

to use these devices would likely also be lacking in these communities. Moving development to mobile computing devices mitigates these complications. There may of course be a lack of familiarity with mobile devices as well, but the more intuitive touch screen interfaces will be easier to master for young children. A move to mobile computing can also benefit children in more developed countries as well, as their first exposure to technology will likely also be in the form of mobile devices or tablet computers [28]. There are of course challenges involved with mobile computing with more issues with input lag, latency, and less memory and processing power. The benefits do outweigh the complications.

Over the past 3 years, the Foundation for Alcohol Related Research (FARR) has been developing and piloting such a cognitive training program tailored to the South African context. The intervention is designed for eventual use on tablets or smartphones that are becoming more ubiquitous even in low-income communities [29]. The FARR game is focused on exercising EFs, particularly attention, inhibition, and working memory. From the outset, it was designed to be suitable for children with little to no computer literacy, to need minimum support and intervention from professionals, and have the possibility to be scaled up as an intervention.

Methods

Overview

We are conducting a feasibility randomized controlled trial (RCT) to evaluate the use of a custom-developed cognitive training program to improve the cognitive function of children aged between 4 and 6 years who were exposed to alcohol in the prenatal stage compared with a control group.

We hypothesize the following:

1. Post intervention, the intervention group will score higher on psychometric assessments of EFs than the control group.
2. At baseline, alcohol-exposed children (both intervention and control groups) will score significantly lower on psychometric assessments of EFs compared with nonalcohol-exposed children (normative group).
3. Post intervention, the intervention group will score higher on psychometric assessments of EFs than the control group, but lower than the normative group.
4. Post intervention, the intervention group will show greater improvement on psychometric assessments of EFs than the control and normative groups.
5. Improvement in game performance will be correlated with improvement on psychometric assessments of EFs.
6. Improvement in psychometric assessments of EFs will be positively correlated with total time spent playing the game.

Research Ethics and Approval

Ethical approval for the protocol has been obtained from the Health Research Ethics Committee at Stellenbosch University (reference number: N16/05/063). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) were used in designing the study and writing of the protocol. A checklist and populated checklist have been provided as per the recommendations. The trial has been registered with the ISRCTN registry (ISRCTN17244156). Should the intervention prove successful, the game will be made available to all participants. This would, however, require the participant to have access to a suitable device as providing participants with tablet computers would not be feasible.

Setting

The RCT will be conducted in the Saldanha Bay Municipal (SBM) area in the Western Cape province of South Africa. Saldanha Bay is the largest natural port in Africa, most of the economic activity in the area is related to fishing, agriculture, and iron exports. There is, however, significant income inequality and an unemployment rate of 17% [30]. FARR has previously conducted a prevalence study in this area, where a prevalence rate of FASD of 64.2 per 1000 was found [31]. FARR subsequently implemented a comprehensive prevention and awareness program between 2013 and 2016 and is currently running an awareness program in the SBM area.

Although the aim of the intervention is to develop cognitive training for children with FASD, it is not possible to identify and diagnose a large group of children with FASD within the study's timeframe. The intervention will thus be evaluated using children who were exposed to alcohol during pregnancy regardless of whether they have received a diagnosis of FASD. To screen for alcohol exposure, we will conduct in-depth interviews with mothers of children who attend Early Childhood Development (ECD) centers in the SBM area.

Eligibility Criteria

Inclusion Criteria

Children aged between 4 and 6 years will be eligible for inclusion. Children must reside in the SBM area and attend or be enrolled in an ECD center.

Exclusion Criteria

Children with a physical disability that will hamper their interaction with the program will be excluded, for example, severe eyesight problems.

Intervention

The efficacy of cognitive training is influenced by the time spent interacting with the program and the difficulty of the tasks presented, especially in terms of whether skills that are not directly trained will improve [18]. In the first step, the specific processes to be targeted were identified using the available literature. In consultation with a software developer, the basic interface and game mechanics were designed, focusing on an intuitive interface and game mechanics that will allow the same interaction to be used with all tasks. In the alpha (initial) version, it is possible to select different tasks to ensure data can be gathered for all stages and tasks. Data that are logged will include the date and time of the play session, the response time per item, and whether the correct response was selected for each item.

The theoretical basis for the game design involves 2 different definitions of *scaffolding* in 2 different contexts. The first refers to work on childhood development and cognitive development. In this context, scaffolding refers to the support of cognitive

development by reducing a complex problem to subproblems, and by solving the subproblems, the ability to solve the complex problem is gained [32]. The game was developed to incrementally increase the demands on various cognitive abilities, with continued successes on one level of difficulty eventually enabling success on a higher level of difficulty.

The second context of scaffolding refers to neuroplastic scaffolding. This term is generally used in connection with age-related cognitive decline [33], but as the target population of this intervention frequently suffers from structural brain abnormalities [2], the same concept of neuroplastic scaffolding should still apply. It refers to compensatory neural activity aimed at supporting damaged, inefficient, or poorly functioning cognitive functions. Scaffolding happens through recruitment of additional prefrontal cortex activity, neurogenesis (formation of new neuronal connections), and distributing cognitive processing over various brain structures. This theory supports the hypothesis that practice and training can enhance the process of scaffolding [34]. This was the driving principle behind the conceptualization and design of the game.

To try and ensure long-term engagement with the game, meta-game elements have been added to the game in the form of a progress bar and animations that only appear once you have completed a set number of tasks. There will be no external rewards or incentives for playing. This is intentional as a key design consideration is that it should be fitting for context where no external rewards would be available. Tasks were designed to require effortful use of inhibitory control, cognitive planning, set shifting, and working memory for completion. The tasks have been designed in such a way that regardless of which function is being targeted, the interface and interaction with the participant does not change. If the interaction remains the same, it is easier to switch seamlessly between stages to maintain optimum difficulty.

The game we have designed (1) is easy to use regardless of computer literacy, (2) logs performance on various metrics (response times and error rates), (3) has continuously adaptive difficulty levels to maintain a suitable level of challenge, and (4) will be open access (free to distribute). Before making the intervention available, it is necessary to test whether it does in fact have an impact on cognitive development.

An alpha version of the program was piloted on a sample of normally developing children to ensure that the tasks escalate in difficulty. This provided an opportunity to ensure that the timing of visual stimuli is age appropriate for the proposed sample's age. The pilot also provided normative data on participant performance to guide further development of the program.

Control Condition

Children in the control group will not be receiving any intervention. They will be assessed at the start of the study and there will be no further interaction with project staff or community workers until the intervention has run its course and they receive the follow-up assessment.

Recruitment

Trained community workers will contact mothers through the ECD centers. They will obtain informed consent to conduct a maternal interview and to include their child in the study in one of the 3 groups. The interviews will include demographic questions and information on alcohol use during pregnancy. The interview questionnaire has been used extensively in prevalence studies in South Africa to identify whether children were exposed to alcohol during pregnancy [3,31-33]. The interview will indicate if a mother consumed alcohol during pregnancy, and it will give an indication of the amount of alcohol consumed. If a child was exposed to more than 3 units of alcohol in 1 drinking session, they will be classified as *alcohol exposed*. This is in line with the latest FASD diagnostic guidelines [2].

As alcohol-exposed children are identified, they will be allocated to the intervention or control group using block randomization with a block size of 8. The randomization will be done by the primary investigator using assigned study numbers to blind them to the participants' identity. Once a block has been filled, the 4 participants allocated to the intervention will start the intervention. The normative group will be recruited from children not exposed to alcohol during pregnancy on the basis of the maternal interviews using random number tables. A list of study numbers will be created and entries in the list will be selected based on the tables [35]. The primary investigator will be blind to participants' identities during this operation.

Data Collection

The maternal interview will be conducted by community workers. They have extensive experience in conducting this particular interview as they interviewed mothers during previous prevalence studies using the same tool. Any additional community workers required will be trained by the primary investigator. After the training, they will conduct mock interviews with their fellow community workers.

The neurodevelopmental assessments will be conducted by a psychometrist with experience in assessing by using the NEuroPSYchological Assessment, Second Edition (NEPSY-II). The psychometrist will also have extensive experience working with children exposed to alcohol during pregnancy and have participated in FASD prevalence studies.

The intervention will be overseen by trained community workers. They will be trained on how the game should be played and instructed on how they should interact with the children after they have mastered playing the game on their own. The community workers will also be trained on how to copy and secure the game logs kept on the tablet computers.

Study Procedures

Alcohol-exposed children, as assessed by maternal interviews, will be randomized into an intervention or a control group with 40 participants in each group, using block randomization. The maternal interview will contain questions regarding alcohol use just before and during pregnancy, including the number of standard units of alcohol consumed, with 3 standard units being the threshold for determining alcohol exposure. A group of 40

unexposed children will be randomized in a group to provide normative data using individual randomization. An overview of the study design is shown in Figure 1. As the participants are drawn from a low-SES and resource-poor environment, the performance of the normative group will serve as a more suitable gauge of cognitive development in the participants' specific contexts. This will enable us to better interpret the results of the neurodevelopmental assessments.

The SPIRIT schematic is shown in Table 1. Baseline assessments examining cognitive function will be conducted with all 3 groups. The intervention group will then play the FARR game twice a week for 6 months (40 play sessions in total). Post intervention, all 3 groups will receive follow-up cognitive assessments. Data gathered by the game will also be collected from the intervention group. All participants will start the intervention at the same level of difficulty. They will be given the opportunity to play the game during hour-long sessions facilitated by community workers. Play will, however, be self-directed; participants will be encouraged to play but will be allowed to stop at any time during a session. As participants log into the devices, they will be able to continue at the difficulty level they had previously reached.

There are 4 different stages in the game of increased complexity. After 10 trials in a stage, a participant automatically moves on to the next for 10 trials. After the fourth stage, participants start at the first stage again. The difficulty of each stage varies independently based on a participant's performance. Getting 8 or more correct increases difficulty, getting fewer than 4 correct decreases difficulty, and otherwise the difficulty remains the same.

Figure 1. Overview of study design.

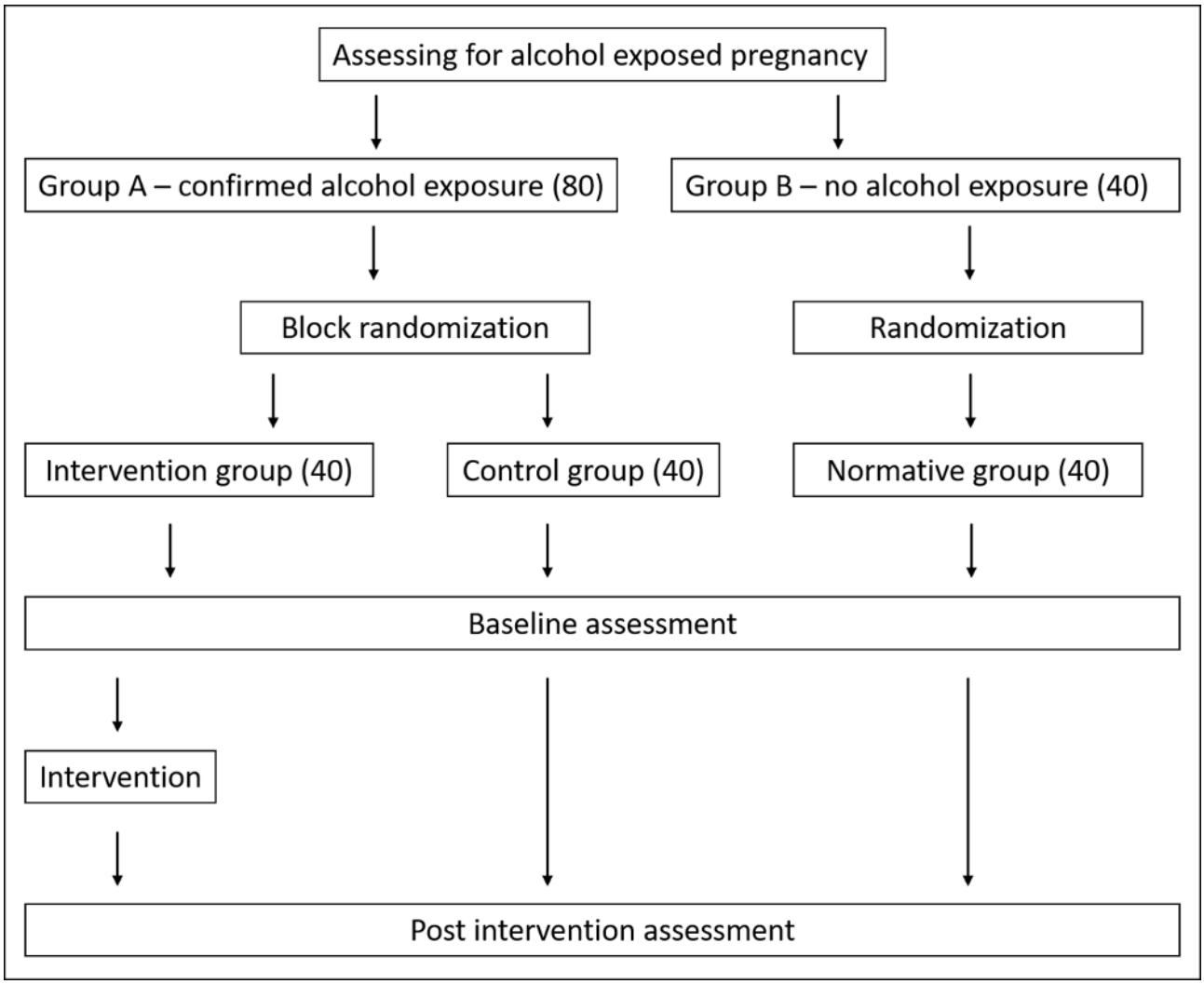

Table 1. A trial schedule per the Standard Protocol Items: Recommendations for Interventional Trials schematic.

Timepoint	Study period			
	Enrollment	Allocation		
	$-t_1$	0	t_1	t_x
Enrollment				
Eligibility screen	X	—[a]	—	—
Informed consent	X	—	—	—
Maternal Interview	X	—	—	—
Allocation	—	X	—	—
Interventions				
FARR[b] game	—	—	X	—
No intervention control group	—	—	X	—
No intervention normative group	—	—	X	—
Assessments				
NEPSY-II[c] psychometric assessment	—	X	—	X
Data logged by FARR game	—	—	—	X

[a]Not applicable.

[b]FARR: Foundation for Alcohol Related Research.

[c]NEPSY-II: NEuroPSYchological Assessment, Second Edition.

Measures

The primary outcome is EF, as measured using the NEPSY-II psychometric assessment score. The secondary outcomes are (1) game performance, as measured in the game log files, (2) reaction time, and (3) increase in the level of difficulty of the task.

Additional demographic data will be gathered during the recruitment process. In addition to alcohol use, data will be gathered on age, gravidity, parity, years of schooling, and household income.

All participants will be evaluated using a selection of subtests of the NEPSY-II that measure executive functioning and working memory. Cognitive function, focusing on EFs, will be measured using the NEPSY-II [36]. The NEPSY-II is a compendium of tests based on the Luria theoretical approach to neurological assessment. It is individually administered and has been shown to be successful in diagnosing a range of childhood disorders. The subtests of this test can also be selected based on the specific domains to be tested [37].

Scores obtained on the subtests of the NEPSY-II are compared with the scores of a normative group based on age. The normative group of the NEPSY-II was selected to closely match the US population between 3 and 16 years of age [38]. This group will differ significantly from the populations of interest in this study; however, the NEPSY-II is relatively insensitive to language and culture differences. Although the results need to be interpreted cautiously, the test remains clinically useful [39]. Insensitivity to language is an important feature as the study sample will be drawn from a predominantly Afrikaans-speaking community, which could affect test performance [40].

In the standardization of the NEPSY-II, subtests showed adequate-to-high internal validity. There was no significant practice effect with re-administration of the test in a short space of time (around 3 weeks), supporting its use for both the pre- and postintervention assessments in this study [41]. Inter-rater agreement was high on both the objectively and more subjectively scored test, and the reliability of subtests remained stable [38]. The inclusion of the third group of children not exposed to alcohol in pregnancy will help guide the interpretation of results.

The NEPSY-II uses separate batteries for children aged 3 to 5 years and children aged 6 to 16 years. Between the ages of 3 and 5 years, not all subtests can be administered. We will be focusing on the subtests that are the same for all participants from 4 to 6 years. Participants who are aged 6 years at baseline and/or at the postintervention assessment will be tested on 4 additional subtests to provide a broader base for comparing game tasks and EFs (see Table 2).

Table 2. Subtests to be assessed.

Domain	Attention and executive function	Language	Memory and learning
All ages	Statue	Comprehension of instructions	Memory for designs
All ages	__[a]	—	Narrative memory
All ages	—	—	Sentence repetition
6-year-olds only	Auditory attention	—	—
6-year-olds only	Design fluency	—	—
6-year-olds only	Inhibition	—	—
6-year-olds only	Inhibition naming	—	—

[a]Not applicable.

Game Log Files

Additional data will be obtained from the log files generated by the game. The file will record error rates and response times for all tasks. Each child will be allocated a numbered tablet or a profile on a specific tablet, depending on what proves the most practical, and the log file will then be associated with their study number.

Sample Size

A total of 120 participants will be recruited and randomized to one of 3 study arms. This is in line with the sample sizes of previous studies looking at FASD and cognitive functioning [9,19,39]. Previous studies of this nature showed a medium effect size [42-45]; however, owing to the differences in method and there not being interventionists involved in the training sample, size calculations were done for a small (d=0.2) effect size. With a significance level of .05, 120 participants in 3 groups would yield a statistical power of 0.79 for the repeated measures multivariate analysis of variance (MANOVA) comparing the performance between the 3 groups.

There are approximately 46 ECD centers, and in SBM area, 1593 children aged between 3 and 5 years have enrolled at these centers and 1635 6-year-olds have enrolled in Grade R [46]. Assuming a prevalence rate of 24% of consuming alcohol during pregnancy on the basis of a prevalence study conducted in SBM area [31], it should be possible to reach the desired sample size through 400 interviews.

Data Analysis

For the primary hypothesis, the postintervention scaled scores of the intervention group will be compared with those of the control group. This will be done using a MANOVA with group membership as the predictor variable and the scaled scores of the 5 NEPSY-II domains (see Table 1) as outcome variables. Discriminant analysis will be done on the outcome of the MANOVA with the domain scores as predictor variables and group membership as outcome variables.

During further analysis, the baseline NEPSY-II scaled scores of the intervention and control groups will be pooled and compared with the scores of the normative group. This will also be done using a MANOVA with group membership as the predictor variable and the scaled scores of the 5 NEPSY-II domains (see Table 1) as outcome variables. Discriminant analysis will again be done on the outcome of the MANOVA with the domain scores as outcome and group membership as predictor variables.

Postintervention NEPSY-II scaled scores (see Table 1) of the intervention, control, and normative groups will be compared using a MANOVA. Group membership will be the predictor variable, and domain scores will be the outcome variables. Discriminant analysis will be conducted with the domain scores as outcome variables and group membership as predictor variables.

Difference scores between baseline and postintervention assessments will be calculated for all participants. These scores will be compared using a MANOVA with group membership as the predictor variable and changes in domain scores (see Table 1) as outcome variables. Discriminant analysis will be done on the results with changes in domain scores as outcome and group membership as predictor variables.

For the secondary hypothesis, the improvement in game performance will be quantified as how many difficulty levels a participant has successfully completed in each of the 3 different stages of the game. This will then be correlated with performance in the NEPSY-II domain scores in a covariance matrix using the Pearson correlation coefficient. A separate analysis will be done including only 6-year-old children using the additional domains tested (see Table 1).

Additional exploratory analyses will be done comparing the demographic information of the 3 groups. These data will be drawn from the maternal interview. Demographic data on the mothers of the alcohol-exposed children (both intervention and control groups) will be pooled and compared with nonalcohol-exposed children to ascertain if there were significant differences between the 2 groups. This will be done using 2 tailed t tests for independent samples. To account for family-wise errors, Bonferroni-adjusted values will also be calculated. The variables to be analyzed are age, gravidity, parity, years of schooling, and income. Tobacco and drug use will also be compared among the alcohol-exposed and nonalcohol-exposed groups using a chi-square test.

Further exploratory analysis will be done on the game logs. Reaction time in the various stages of the game will be used to conduct an exploratory factor analysis. Looking for common variations among the various game metrics may unearth

underlying variables that better explain which EFs are associated with which game tasks. For each participant, their reaction times for the highest level they successfully complete will be used. Using regularized exploratory factor analysis owing to the small sample size, we can examine whether the conceptually different tasks do in fact target different EFs.

Results

At the time of submission, the majority of recruitment was completed, and the intervention phase had already started for some participants.

Discussion

To the best of our knowledge, this study is the first of its kind in the South African context. Although there is evidence for the use of cognitive training games to improve executive functioning in children with FASD, the feasibility of such an approach in a resource-poor context has not been evaluated. This study will provide data on both the general approach of cognitive training games in the South African context and the feasibility of our custom-developed game. These data will guide decision making on whether the current program is suitable for the purpose of remediation, whether it needs redesign, whether the method holds promise but requires a different game or program, and finally whether computer-based cognitive training is a feasible strategy at all.

Should the trial show promising results, the next step would be to use the results of this study to inform further development. Further trials with more participants and a control group receiving some form of intervention would provide support for scaling up the intervention. In addition, the intervention can then be made available to all interested parties free of charge to provide at least some basic form of evidence-based remediation. If there are strong correlations between the NEPSY-II scores and the game tasks, further studies could evaluate whether the game could be used as a screening tool for difficulties with EFs.

As the game does not use language in any of the tasks, it can be used outside of the South African context with ease. With further development, it will also be available for more devices (smartphones) and not only for tablet computers. It could therefore be a valuable tool in other countries where remedial resources are not available, and it can be used by caregivers and parents to support existing remedial efforts. The nature of the cognitive training does not limit its use to FASD remediation. If children exposed to alcohol show improvement, theoretically, children with cognitive deficits with different etiologies will also benefit.

Regardless of the trial outcome, this study will add significantly to the literature on executive functioning in children with PAE. It will also provide more insight into how the environment and development of children with PAE differs from children who were not exposed to alcohol in utero.

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Conflicts of Interest

Authors JGL and LO are employed by the FARR that receives additional funding from aware.org for additional projects. FARR is a nonprofit organization and the FARR game will not be monetized.

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Abbreviations

ECD: Early Childhood Development
EF: executive function
FARR: Foundation for Alcohol Related Research
FASD: fetal alcohol spectrum disorder
MANOVA: Multivariate analysis of variance
NEPSY-II: NEuroPSYchological Assessment, Second Edition
PAE: prenatal alcohol exposure
RCT: randomized controlled trial
SBM: Saldanha Bay Municipal
SES: Socioeconomic status
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effectiveness of a Walking Program Involving the Hybrid Assistive Limb Robotic Exoskeleton Suit for Improving Walking Ability in Stroke Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: Gait disturbance often occurs in stroke survivors. Recovery of walking function is challenging, as some gait disturbance due to hemiparesis often remains even after rehabilitation therapy, presenting a major obstacle towards regaining activities-of-daily-living performance and achieving social reintegration.

Objective: This study aims to clarify the effectiveness of a walking program involving the wearable Hybrid Assistive Limb (HAL-TS01) robotic exoskeleton for improving walking ability in stroke patients with hemiparesis and stagnant recovery despite ongoing rehabilitation.

Methods: This is a multicenter, randomized, parallel-group, controlled study (HAL group, n=27; control group, n=27). The study period includes preintervention observation (until stagnant recovery), intervention (HAL-based walking therapy or conventional rehabilitation; 5 weeks), and postintervention observation (2 weeks). Following provision of informed consent and primary registration, the patients undergo conventional rehabilitation for preintervention observation, during which the recovery of walking ability is monitored to identify patients with stagnant recovery (based on weekly assessments using the 10-meter maximum walking speed [MWS] test). Patients with an MWS of 30-60 m/minute and insufficient weekly improvement in MWS undergo secondary registration and are randomly assigned to undergo HAL-based walking therapy (HAL group) or conventional rehabilitation (control group). The primary outcome is the change in MWS from baseline to the end of the 5-week intervention.

Results: This study began in November 2016 and is being conducted at 15 participating facilities in Japan.

Conclusions: Assessments of walking ability vary greatly and it is difficult to define the threshold for significant differences. To reduce such variability, our study involves conducting conventional rehabilitation to the point of saturation before starting the intervention. Stagnation in the recovery of walking ability despite conventional rehabilitation highlights the limits of current medical care. The present study may bring evidence that HAL-based therapy can overcome such limitations and induce added recovery of walking ability, which would promote the use of HAL technology in the clinical setting.

Trial Registration: UMIN Clinical Trials Registry UMIN000024805; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000028545

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KEYWORDS

Hybrid Assistive Limb (HAL); gait training; stroke; hemiparesis

Introduction

At stroke onset, more than 60% of patients have gait disturbance and about 50% are unable to walk [1,2]. Recovery of walking function is generally a long and arduous process [1,3,4]. Current rehabilitation strategies for poststroke gait disturbance are quite effective, but patients with severe gait disturbance may not fully recover their walking ability. Furthermore, such gait disturbance is a major obstacle towards recovering activities-of -daily-living (ADL) performance and achieving social reintegration.

The Hybrid Assistive Limb (HAL) manufactured by Cyberdyne Inc. (Tsukuba, Japan) is a robotic exoskeleton that aids body movements by detecting and enhancing bioelectric signals to the muscles. When a person tries to move a muscle, a signal is transmitted from the brain through the spinal cord and motor neurons to said muscle, causing the musculoskeletal system to move. This process is accompanied by weak bioelectric signals detectable at the surface of the skin. The HAL was developed to read such bioelectric signals and help with movement per the person's intentions [5,6]. Different hypotheses have been proposed about the effects of HAL therapy, including the interactive bio-feedback hypothesis and neural plasticity [7], but these remain unproven. Clinical studies conducted in Japan confirmed the clinical effects of HAL therapy and, in November 2015, a leg-type bipedal HAL was approved as a new medical device for managing spinal muscular atrophy, spinal and bulbar muscular atrophy, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease, distal myopathy, inclusion body myositis, congenital myopathy, and muscular dystrophy, apart from this clinical trial.

Whereas the mechanisms underlying the therapeutic action of the HAL have not been completely clarified, some researchers believed that HAL therapy is superior to standard robot-assisted training because it supplies better feedback and supports natural motions. Several earlier studies have examined the effectiveness of HAL-based walking exercises for alleviating gait disturbance in stroke patients. In a study on the stages of recovery after stroke, Kawamoto et al [8] showed that 16 sessions of HAL-based walking exercise increased walking speed and improved balance ability. In a randomized pilot trial, Watanabe et al [9] also found that 12 sessions of HAL-based walking exercise were more effective than conventional walking rehabilitation in terms of improving the functional ambulation category. Thus, these papers have confirmed the feasibility of HAL for clinical application.

Unlike prior studies, the present trial is designed to examine the effectiveness of HAL-based walking exercise in stroke patients with stagnant recovery under conventional rehabilitation. This is necessary because there is considerable variability on how recovery is assessed and what constitutes a meaningful rate of improvement. Therefore, the present study includes a preintervention observation period during which conventional rehabilitation for walking ability is performed until stagnation of recovery is noted. The fact that some patients no longer experience an improvement in walking ability despite continuing rehabilitation therapy highlights the current limits of conventional rehabilitation programs. The present study may bring evidence that HAL-based intervention can induce added recovery of walking ability in such patients, which would promote the use of HAL-based walking therapy in the clinical setting.

Methods

Study Objectives

The present study aims to clarify the efficacy of a HAL-based walking program versus conventional rehabilitation focused on restoring walking ability in patients with hemiparesis due to stroke.

Study Design

The present study is designed as a multicenter, randomized, parallel-group, controlled trial. Our aim is to enroll 54 participants (27 in the HAL group and 27 in the control group) by December 2019. The patients have been recruited since November 2016, and the intervention is being conducted at 15 participating facilities.

The study has three phases (preintervention observation, intervention, and postintervention observation, as seen in Figure 1). Because of the evaluation of treatments that improve walking ability, this clinical trial focuses on walking ability rather than the severity of stroke to evaluate the patients.

The primary outcome of the study is the change in maximum walking speed (MWS) on the 10-m walk test from baseline to the end of the 5-week intervention. However, patients' ADL or social reintegration are the true outcome, with walking ability selected as the surrogate outcome that was strongly associated with ADL or social reintegration [10]. In order to clarify whether the HAL-based walking program can boost walking ability once recovery has become stagnant despite ongoing conventional rehabilitation, the intervention is indicated only for patients who exhibit stagnant recovery of MWS, which is defined as insufficient weekly improvement in the MWS during the preintervention observation period. In addition to MWS, walking ability is also evaluated based on a patient's ability to walk independently, but in this clinical trial the patients were only assessed with MWS because of its quantitative nature. The MWS values are measured every week and then smoothed over the current and previous two weeks (Standalone Equation 1) (Figure 2). The weekly rate of change in the smoothed MWS is obtained to determine the recovery rate (Standalone Equation 2). Stagnant recovery of MWS is then defined as <10% improvement compared to the previous week. Patients with an MWS of 30-60 m/minute and stagnant recovery of MWS are randomly assigned to either the control group or the HAL group.

Figure 1. Study design. This multicenter, randomized, parallel-group, controlled study has three phases (preintervention observation, intervention, and postintervention observation). Following primary registration, the patients undergo conventional rehabilitation and are monitored to detect stagnant recovery. Upon secondary registration prior to the intervention, the patients are randomized to undergo conventional rehabilitation aimed at regaining walking ability (control group), or a walking program involving the use of the Hybrid Assistive Limb (HAL) robotic exoskeleton (HAL group).

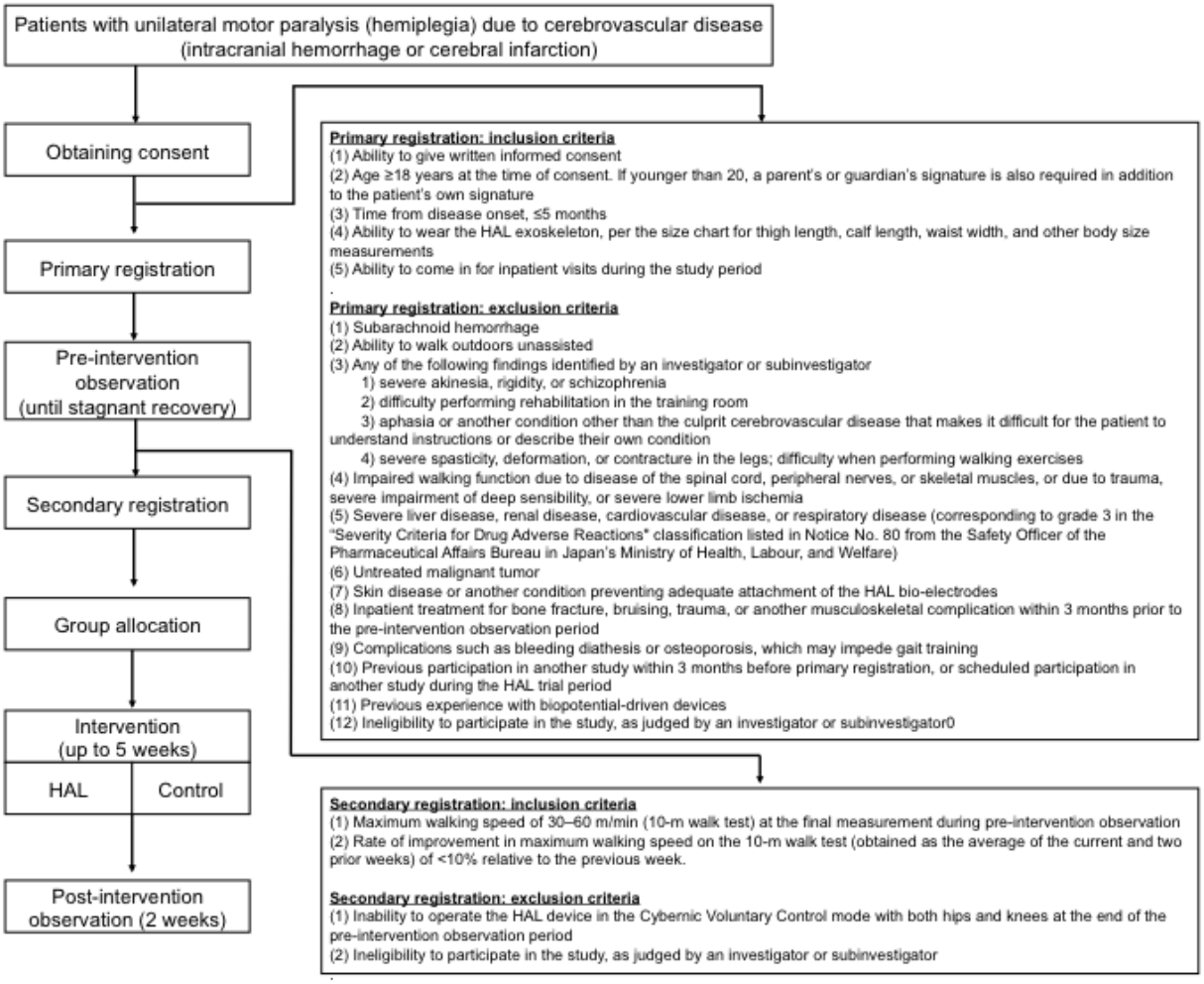
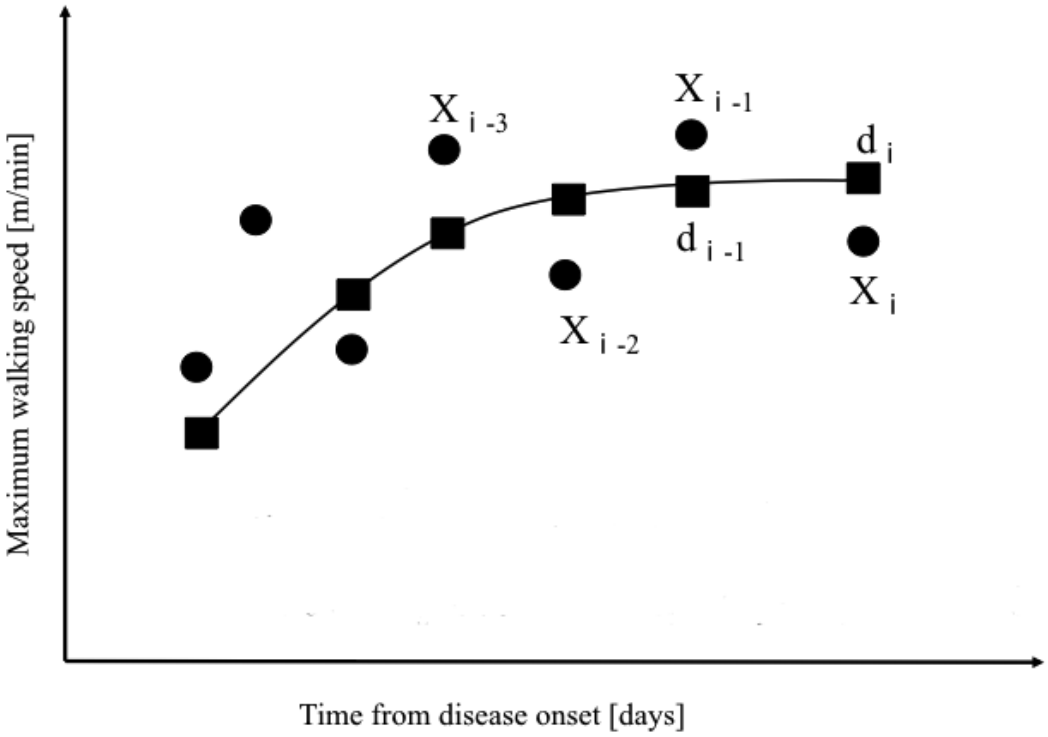


Figure 2. Method for smoothing the value of the maximum walking speed on the weekly 10-m walk test. MWS: maximum walking speed. (X_i): MWS value measured for week i. (d_i): Smoothed MWS value for week i, obtained as a moving average of the MWS values measured for weeks i, i-1, and i-2.



This protocol has been approved by the Central Institutional Review Board of the Ibaraki Clinical Trial & Research Network. The research leader has notified the regulatory authorities with respect to the design and schedule of the clinical trial and has registered the study with the University Hospital Medical Information Network (UMIN trial registration number: UMIN000024805) prior to starting patient registration. Candidate patients are enrolled only upon supplying written informed consent for participation.

Registration and Randomization

Upon supplying written informed consent, the patients were evaluated for eligibility according to the inclusion and exclusion criteria for primary registration. Registered patients who had completed the preintervention observation were evaluated for eligibility according to the inclusion and exclusion criteria for secondary registration. Stratified randomization was conducted, with MWS at allocation (<45 or ≥45 m/minute), age at the time of consent (<60 or ≥60 years), and the intervention center as the stratification factors. Data program and randomization program were served by CIMIC Co., Ltd. (Tokyo, Japan).

Inclusion and Exclusion Criteria

Two sets of inclusion and exclusion criteria were employed in this study, namely at the time of primary and secondary registration. The inclusion criteria for primary registration included: (1) hemiparesis due to stroke; (2) age ≥18 years; (3) ≤5 months from stroke onset; and (4) ability to give written informed consent. Furthermore, patients had to be able to come in for inpatient evaluations during the study period and had to be able to wear and use the HAL robotic exoskeleton. Patients with subarachnoid hemorrhage, which involves bleeding in the subarachnoid space and is thus distinct from brain hemorrhage or cerebral ischemia, were excluded. Patients who achieved enough improvement in walking ability and become able to walk outdoors unassisted were also excluded, as they might not have benefitted as much from HAL therapy. For safety reasons and due to the specific nature of the device and training program, patients with any of the following conditions were also excluded: (1) severe akinesia, rigidity, or schizophrenia; (2) difficulty performing rehabilitation in the training room; (3) a condition other than the culprit cerebrovascular disease that makes it difficult for the patient to understand instructions; (4) impaired walking function due to a disease of the spinal cord, peripheral nerves, or skeletal muscles, or due to trauma, severe impairment of deep sensibility, or severe lower limb ischemia; or (5) other severe uncontrollable diseases.

The inclusion criteria for secondary registration were: (1) insufficient rate of weekly improvement in MWS (smoothed value) during preintervention observation (<10% improvement relative to the previous week); and (2) MWS of 30-60 m/minute at the final measurement during preintervention observation. Among patients who are able to wear the HAL robotic suit, we excluded those unable to operate it in the Cybernic Voluntary Control mode with both hips and knees, in which it can assist with movement in accordance with the person's intentions.

Discontinuation From the Study

Investigators and other persons involved are permitted to discontinue the study if consent is withdrawn, if it is discovered that an exclusion criteria is satisfied, if an adverse event or another circumstance renders the patient unable to participate in the intervention for ≥1 week at a time, or if it is deemed

difficult to continue the study and valid to discontinue it for efficacy or safety reasons.

Intervention

Following primary registration, the patients underwent conventional rehabilitation and were monitored to detect stagnant recovery (preintervention observation). Upon secondary registration prior to the intervention, the patients were randomized into two groups (intervention). Patients assigned to the control group underwent conventional rehabilitation aimed at restoring walking ability for 5 weeks, which did not involve the use of the HAL. Patients assigned to the HAL group underwent a rehabilitation program involving walking exercises performed while wearing the HAL robotic exoskeleton suit for 5 weeks. All patients underwent a 60-minute session of conventional rehabilitation followed by 20 minutes of rehabilitation over ground, which aimed to improve walking ability. This was conducted while wearing the HAL robotized suit (in the HAL group) or without wearing the HAL suit (in the control group), depending on group allocation. The HAL walking program took place for a net 20 minutes, except for the time involved with attaching and detaching the HAL. Following an intervention period, the patients continued conventional rehabilitation for another two weeks (postintervention observation). Postintervention observation is meant to evaluate whether the patient can maintain their improved walking ability, though it is short.

Conventional rehabilitation consists of 80-minute sessions of exercises designed to improve muscle tone in the paralyzed limbs, as well as muscle strength and coordination, thus enhancing basic motor skills, balance, and walking ability in preintervention observation and postintervention observation (Textbox 1). Conventional rehabilitation is conducted, in principle, 5 days per week.

Textbox 1. Conventional rehabilitation program.

- Rehabilitation aimed at restoring walking ability:
  - Walking exercise (adaptive walking, outdoor walking, stair climbing/descending)
  - Treadmill walking exercise (with body weight support)
  - Endurance training (cycle ergometer exercise)
- Other rehabilitation therapy

Assessment and Study Endpoints

The primary outcome is the change in MWS from baseline (ie, right before the intervention) to the end of the 5-week intervention. The secondary outcomes include: (1) the change in mean step length and the change in average step rate at MWS; (2) the change in single-leg support time expressed as a percentage of the gait cycle at MWS; (3) the change in maximum distance walked over the course of 6 minutes; (4) the change in functional ambulation category; (5) the change in Berg Balance Scale score; and (6) the change in leg score upon Fugl-Meyer Assessment. Multimedia Appendix 1 provides an overview of the assessment schedule.

Preintervention observation during conventional rehabilitation is conducted until stagnant recovery. Intervention with HAL-based walking therapy or conventional rehabilitation is conducted for up to 5 weeks.

Safety was assessed in terms of the nature and frequency of adverse events occurring between the start of the intervention until the end of the postintervention observation period. The circumstances and frequency of HAL malfunction are also recorded.

A physical therapist (PT) group operating HAL and a PT group evaluating patients were created at each facility, and these two groups did not share patient information. A four-hour briefing session on protocols and measurement methods was held at all centers to equalize the quality of measurement methods. Attendance of this briefing session was a requirement for the staff to take part in this clinical trial.

Sample Size

The main purpose of this study is to confirm the superiority of the HAL-based walking exercise (HAL group) over conventional rehabilitation focused on improving walking ability (control group), and the main outcome is MWS improvement. Based on a previous clinical study [10] that compared a HAL group and a non-HAL group, and taking into consideration the fact that this is a multicenter study, the clinically meaningful between-group differences in mean MWS and associated standard deviation were conservatively estimated at 9 m/minute and 11 m/minute, respectively. A minimum sample size of 50 participants (25 patients per group) is expected to provide a power of 0.8 for detecting such differences, with two-sided significance of 0.05. Assuming a dropout rate of around 5%, we aim to include 54 participants (27 per group).

Statistical Analysis

The efficacy of HAL-based therapy will be analyzed using the full set of data based on the intention-to-treat principle, and using the per-protocol set. The change in MWS from baseline (right before intervention) to week 5 of the intervention, which is the primary outcome, will be compared between the HAL group and the control group using a mixed model, repeated-measures analysis that includes group and intervention period (weeks 1-5) as factors, and group × period interaction, baseline MWS, and age as covariates. The change in mean step length and the change in average step rate at MWS will be similarly analyzed. Other secondary endpoints at 5 weeks will be analyzed using analysis of covariance, which will include group as a factor, and relevant baseline values and age as covariates. The number and percentage of patients who develop

adverse events will be summarized for each group and compared between the two groups using Fisher's exact test. The level of significance is set at 0.05 for all analyses.

Results

This study began in November 2016 and is being conducted at 15 participating facilities in Japan. The study is in progress and the patient enrollment period is scheduled to end in December 2019.

Discussion

This study is being conducted in Japan as a doctor-initiated clinical study to verify the effectiveness of robot-assisted therapy in the wider context of facilitating effective social reintegration of patients with stroke. Therefore, if the study can provide evidence of the superiority of the HAL-based walking exercise over conventional rehabilitation therapy, this would promote the use of HAL-based therapy in clinical practice.

The use of HAL-based exercise to restore motor ability after hemiparesis caused by stroke is likely to have the following medical and social effects: (1) improved motor ability due to recovery of central nervous function through HAL-assisted feedback of active, repeated motion; (2) reduced duration of hospitalization and rehabilitation; (3) fewer sequelae and reduced load on care givers; (4) amelioration of muscle weakness, muscle atrophy, and reduced joint range of motion caused by disuse, as well as better maintenance of ADL performance; and (5) compared to conventional assistance tools, HAL would provide more functionality to reduce residual sequelae such as impaired motor function in the limbs. To clarify these matters, it is necessary to design new study protocols that account for differences in underlying pathology, including symptoms and disease stage. It is also important to prove the effectiveness of the HAL-walking program in this clinical trial.

Rehabilitation is often provided for gait disturbance due to hemiparesis in patients with stroke. However, depending on the severity of such a disturbance, the patients may experience stagnation in their recovery of walking ability and fail to become capable of unassisted walking. A previous clinical study [11] reported that the HAL-based walking program helped increase walking ability in patients with stagnant recovery, suggesting that HAL-based walking exercise can overcome the limitations of conventional rehabilitation and boost walking ability even in patients with stagnant recovery. Considering that walking ability is a major factor in ADL function [10,12-15], benefits conferred by the HAL-based walking program would contribute greatly to enhancing ADL function.

In our present study, stagnant recovery of walking ability was assessed during a preintervention observation period, and only patients who showed insufficient weekly improvement continued to the intervention. This approach will allow us to determine whether the HAL-based walking program can boost walking ability in patients with stagnant recovery despite ongoing rehabilitation.

Because it is a simple and accessible indicator of motor ability during gait, MWS is the most commonly used indicator for assessing walking ability. MWS is also used as an indicator of therapeutic effect, which is helpful for formulating a treatment plan and predicting the prognosis of rehabilitation for impaired motor function in elderly patients or patients with stroke. The minimal difference in MWS that is clinically significant during recovery after stroke has been reported at 8.4 m/minute by Perera et al [16] and at 9.6 m/minute by Tilson et al [17]. While stagnant recovery was often described in studies assessing walking ability or ADL function in patients with stroke [1,2,18], no consensus has been reached on a method for defining the threshold for recovery stagnation. An earlier study defined recovery stagnation in terms of the weekly rate of improvement in MWS, leading to the formulation of guidelines. Moreover, MWS is a useful parameter in the context of social reintegration, which is facilitated through improvement of walking function in patients who are capable of unassisted walking in the home but not outside. Therefore, we set two MWS-based inclusion criteria for the secondary registration. Prior research suggests that the cut-off value for walking speed allowing restricted community walking is 0.4 m/second (24 m/minute), while the cut-off allowing unrestricted community walking is 0.8 m/second (48 m/minute) [2,10,19]. Schmid et al also reported that the mean walking speed of individuals capable of restricted community walking was 25.8-47.4 m/minute, compared to 48-72 m/minute for those capable of unrestricted community walking [10]; however, the above values refer to walking at a comfortable speed. An earlier report indicated that MWS is approximately 1.32 times higher than the comfortable walking speed, irrespective of walking speed [2]. Therefore, the MWS cut-offs for restricted and unrestricted community walking would be 31.7 and 63.4 m/minute, respectively. These values are close to those reported by a study from Japan, which found that the mean MWS for individuals restricted to indoor walking is 33.6 m/minute, compared to 61.8 m/minute for those capable of unassisted community walking [13]. Therefore, one of the inclusion criteria for secondary registration was MWS of 30-60 m/minute. We believe that one of the goals of HAL treatment is to improve the walking ability of patients with community walking and to restore them to society. Furthermore, we included the 6-minute walking distance as a secondary outcome, because this parameter was recently reported to be more suitable than MWS for evaluating walking ability and ADL function [20].

The duration and number of interventions are key factors affecting the effectiveness of the device. A review [21] of clinical research on conventional robot-assisted training revealed that many studies included at least 20 training sessions conducted over 4 weeks; of the studies that showed no effectiveness of robot-assisted intervention (versus a control group), two-thirds employed only 10-12 sessions. To date, the best training duration and frequency of robot-assisted training sessions remains unclear. A before-after study by Kawamoto et al [8] revealed that 16 sessions produced an improvement in walking speed. Meanwhile, the study by Watanabe et al [9] employed a 4-week program with 3 sessions per week and 20 minutes per session, for a total of 12 sessions, reporting limited effectiveness (only in terms of improving the functional ambulation category). Taken together, these earlier observations

suggest an impact of reducing the length of training or the number of training sessions. Indeed, a pilot study [11] involving 5 sessions per week for 5 weeks, for a total of 25 sessions, reported an effective improvement in walking speed. Therefore, the present study uses an intervention protocol like that employed in the pilot study [11].

The present study has several limitations. Factors that affect the prognosis of stroke patients with hemiparesis include the extent of sensory impairment, the patient's motivation, assistance from family members, and the structure of the rehabilitation plan. Another limitation is the inability to blind patients or investigators to the intervention after group allocation. The nature of rehabilitation research precludes the implementation of sham interventions, and it is thus impossible to eliminate bias caused by the placebo effect.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Assessment schedule.
[PDF File (Adobe PDF File), 95 KB - resprot_v8i10e14001_app1.pdf]

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Abbreviations

ADL: activities of daily living
HAL: Hybrid Assistive Limb
MWS: maximum walking speed
PT: physical therapist

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Protocol

Targeting the Infant Gut Microbiota Through a Perinatal Educational Dietary Intervention: Protocol for a Randomized Controlled Trial

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Abstract

Background: The early life gut microbiota are an important regulator of the biological pathways contributing toward the pathogenesis of noncommunicable disease. It is unclear whether improvements to perinatal diet quality could alter the infant gut microbiota.

Objective: The aim of this study is to assess the efficacy of a perinatal educational dietary intervention in influencing gut microbiota in mothers and infants 4 weeks after birth.

Methods: The Healthy Parents, Healthy Kids randomized controlled trial aimed to recruit 90 pregnant women from Melbourne, Victoria, Australia. At week 26 of gestation, women were randomized to receive dietary advice from their doctor (n=45), or additionally receive a dietary intervention (n=45). The intervention included an educational workshop and 2 support calls aiming to align participants' diets with the Australian Dietary Guidelines and increase intakes of prebiotic and probiotic foods. The educational design focused on active learning and self-assessment. Behavior change techniques were used to support dietary adherence, and the target behavior was eating for the gut microbiota. Exclusion criteria were age under 18 years, diagnosed mental illnesses, obesity, diabetes mellitus, diagnosed bowel conditions, exclusion diets, illicit drug use, antibiotic use, prebiotic or probiotic supplementation, and those lacking dietary autonomy. The primary outcome measure is a between-group difference in alpha diversity in infant stool collected 4 weeks after birth. Secondary outcomes include evaluating the efficacy of the intervention in influencing infant and maternal stool microbial composition and short chain fatty acid concentrations, epigenetic profile, and

markers of inflammation and stress, as well as changes in maternal dietary intake and well-being. The study and intervention feasibility and acceptance will also be evaluated as secondary outcomes.

Results: The study results are yet to be written. The first participant was enrolled on July 28, 2016, and the final follow-up assessment was completed on October 11, 2017.

Conclusions: Data from this study will provide new insights regarding the ability of interventions targeting the perinatal diet to alter the maternal and infant gut microbiota. If this intervention is proven, our findings will support larger studies aiming to guide the assembly of gut microbiota in early life.

Trial Registration: Australian Clinical Trials Registration Number ACTRN12616000936426; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370939

International Registered Report Identifier (IRRID): DERR1-10.2196/14771

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KEYWORDS

gastrointestinal microbiome; diet; pregnancy; infant; newborn; randomized controlled trial

Introduction

Background

The diversity and composition of the neonatal gut microbiota is garnering interest as a target for the prevention of noncommunicable diseases. The disappearing microbiome hypothesis contends that reduced bacterial diversity over generations results in increased allergic and metabolic disease risk in children [1]. In 1-month old infants, low microbial diversity is associated with an increased risk of later atopic eczema [2], allergic sensitization, allergic rhinitis, peripheral blood eosinophilia [3], and asthma [4]. In addition, differential microbial composition is associated with an increased risk of noncommunicable diseases, including allergic sensitization [3], eczema [2], asthma risk [5], neurodevelopmental outcomes [6], and later adiposity in infants [7]. Hence, novel methods of altering the neonatal gut microbiome are of interest. The influence of poor maternal diet (high fat or low fiber) on offspring gut microbiota has been studied in animals, demonstrating that poor maternal diets disturb offspring gut microbiota [8,9]. To our knowledge, there are no human randomized controlled trials (RCTs) with the primary aim of testing whether the maternal diet can modify the diversity and composition of the infant gut microbiota. Dietary supplementation trials of perinatal prebiotic or probiotic supplements provide a premise for testing this aim, with some studies indicating that these supplements modify the composition of gut microbiota in mothers [10] and infants [11,12]. Importantly, though, a supplementation approach fails to address the quality of the underlying diet. In humans, the prenatal diet has been associated with the composition of the infant gut microbiota [13,14], but it is still unclear whether this relationship is modifiable. Human studies are needed to determine whether infant gut microbiota can be modified through perinatal dietary change.

In murine [8] and primate [9] models, poor-quality prenatal diets disturb vertical transmission of microbiota (from mother to offspring). For example, a prenatal diet devoid of dietary fiber reduced microbial diversity and the abundance of fiber-degrading taxa in mothers and offspring [8]. Low diversity compounded over 4 generations and could not be corrected via a high-fiber diet. Similarly, compared with a low-fat prenatal diet (13% of energy from soya bean oil), a high-fat prenatal diet altered the microbiota of vaginally born primates [9]. This alteration was persistent at 1 year and could not be corrected by weaning offspring onto a low-fat diet [9]. In humans, compared with a low-fat prenatal diet (24% of daily energy from fat), a high-fat (43%) diet during pregnancy was associated with an altered infant gut microbiome, including a depletion of *Bacteroides* persisting to 4 to 6 weeks of age [13]. Taken together, these results suggest that poor-quality diets (such as low fiber, high saturated fatty acid, and high sugar content) during pregnancy and lactation disturb vertical transmission. However, a causal relationship between the maternal diet and neonatal microbial acquisition is yet to be established in humans.

Healthy dietary patterns that are high in fiber and low in fat are associated with higher microbial alpha diversity in adults [15]. Population-based metagenomic analysis indicates that the dietary features that are associated with higher alpha diversity (as measured by the Shannon Index) are frequent fruit and vegetable consumption along with polyphenol-containing tea, coffee, and red wine [16]. Conversely, dietary features associated with low alpha diversity are sugar-sweetened soda, whole fat milk, savory snacking, and a high total energy intake. Across the developed countries, the mean daily intake of fiber for pregnant women is 18 (SD 4.4) g, this is below the recommended ranges (21-28 g depending on country) [17]. Similarly, mean saturated fat intakes of 32.2 (SD 9.1) g/day were 8.5% to 16.5% above the recommended ranges (depending on country) [17]. In Australia, pregnant women have poor diet quality; they neither know nor meet the Dietary Guidelines for all 5 food groups [18-20], but they are motivated and would like further nutritional education [18].

Objectives

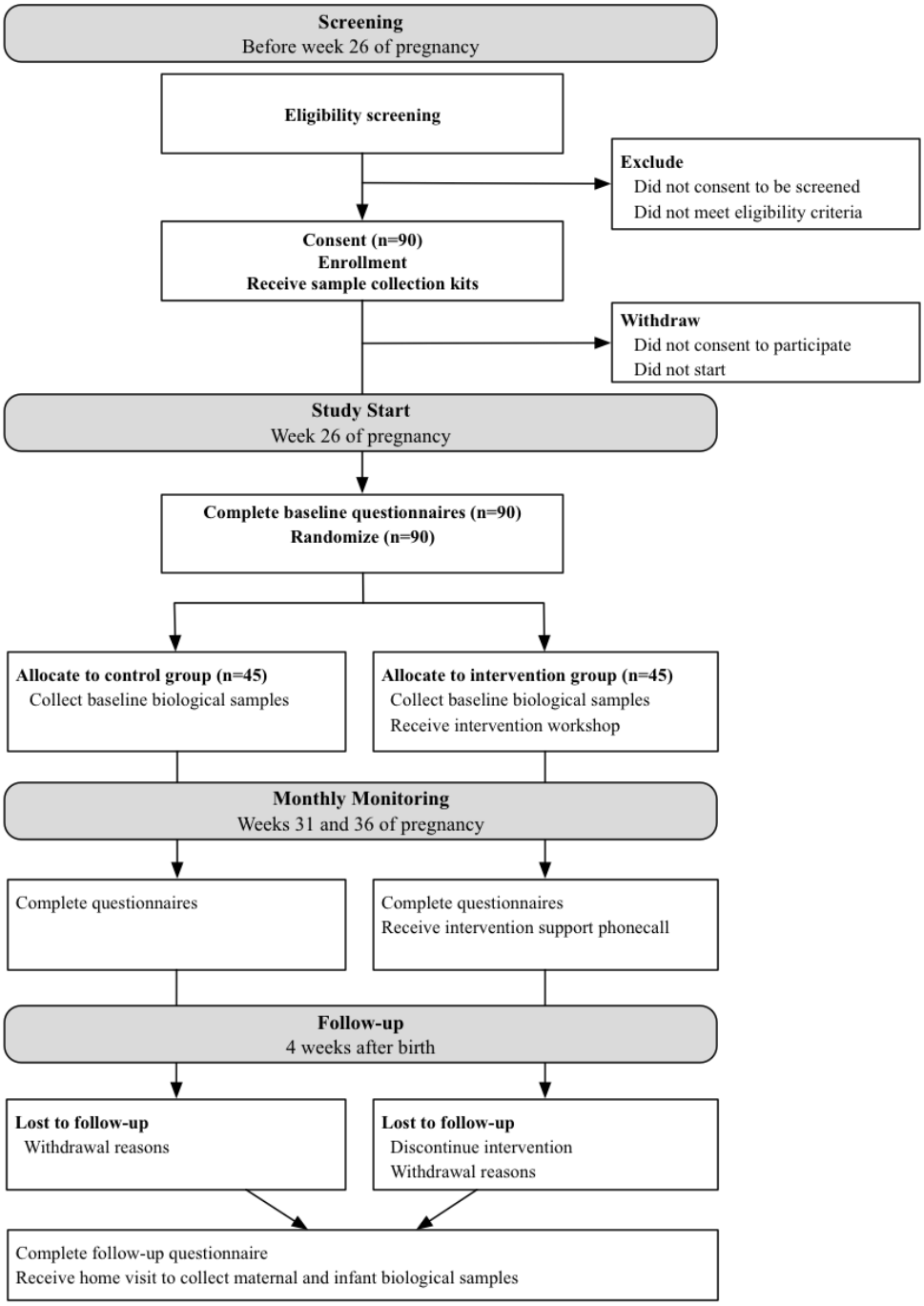
The Healthy Parents, Healthy Kids (HPHK) study (Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN12616000936426) is a prospectively registered open-label, parallel group, RCT of an educational perinatal dietary intervention targeting gut microbiota from the third trimester of pregnancy until 4 weeks after birth. The primary aim is to evaluate whether the dietary intervention alters alpha diversity of the infant gut microbiota 4 weeks after birth.

Secondary aims are to evaluate the efficacy of the intervention in altering microbiota, inflammatory and stress profiles, epigenetic regulation, and maternal diet and well-being. The feasibility and acceptability of the study intervention will also be evaluated. The HPHK study intervention design couples pedagogical theory and educational design (focused on self-assessment and self-efficacy) with Behavior Change Techniques (BCTs) [21] to support efficacy and dietary adherence. A sound educational design is an important, yet seemingly overlooked consideration; first, it ensures that participants are able to *do* the target behavior, second, it helps to mitigate against confusing a true null effect with insufficient learning, and third, it safeguards the literature against spurious findings from poorly designed interventions.

Methods

This protocol was written according to the SPIRIT 2013 statement [22]. See Figure 1 for the study flow diagram.

Figure 1. Study flow diagram. Displays the timing for each activity of the randomized controlled trial.



Primary Hypothesis

The dietary intervention will result in increased microbial diversity (Shannon index) in infants measured 4 weeks after birth, compared with the control group.

Secondary Hypotheses

Microbiota

Using stool samples collected at follow-up, compared with the control group, the intervention group will have (1) dissimilarity in infant stool operational taxonomic units (OTU); (2) higher alpha diversity in maternal stool; (3) dissimilarity in maternal stool OTU; (4) increased relative abundances of genus *Prevotella* in maternal stool.

Diet

Women in the intervention group will (1) improve their diet in accordance with the Australian dietary guidelines; (2) consume a wider variety of foods; and increase intakes of (3) fiber, (4) prebiotic foods, and (5) probiotic foods compared with the control group, and these changes will be sustained throughout pregnancy. The intervention group will reduce intakes of (6) refined processed foods, (7) saturated fat, and (8) total energy compared with the control group.

Further secondary hypotheses for other biological outcomes (ie, short chain fatty acid [SCFA] concentration, inflammation, stress, and epigenetic regulation) and study feasibility are listed in Multimedia Appendix 1.

Primary Outcome Measure

A between-group difference in microbial alpha diversity, measured using the Shannon Diversity Index (which accounts for species richness and evenness) at follow-up (4 weeks after birth) in the infant stool samples.

Secondary Outcome Measures

Infant Microbiota

Between-group differences in other diversity measures including inverse Simpson index (a measure of richness and evenness that is less affected by rare species compared with the Shannon index) and Chao1 (measure of species richness); observed species and phylogenic diversity (measure of diversity including phylogenetic distance); the relative abundance of OTU; beta diversity using measures of between-sample dissimilarity.

Maternal Microbiota

Between-group differences in the relative abundance of OTU; beta diversity using measures of between-sample dissimilarity in response to dietary intake. Baseline-adjusted between-group differences in alpha diversity indices (Shannon Diversity, Inverse Simpson, and Chao1); observed species and phylogenic diversity.

Dietary Intake

Long-term (3-month) maternal dietary quality and variety are evaluated by applying the Dietary Guideline Index 2013 (DGI-13 scores) [23] to the validated Dietary Questionnaire for Epidemiological Studies v2 (DQES) [24], measured at baseline and 4 weeks after birth. DGI-13 scores include a total diet quality score and 13 subscores to evaluate each dietary guideline [25]. Daily macronutrients from the DQES are energy (kilojoules; kJ), protein (kJ), carbohydrate (kJ), fat (kJ), saturated fat (kJ) and fiber (grams). Time-related trends in short-term (2-week) diet quality and intakes of prebiotic and probiotic foods are evaluated using a version of the Simplified Dietary Questionnaire (SDQ) [26] modified to include prebiotic and probiotic foods. SDQ scores include a total diet quality score and comprises a dietary variety score and 9 subscores evaluating each guideline [25], along with 2 additional scores for prebiotic and probiotic food intake.

Further secondary outcome measures for other biological outcomes and study feasibility are listed in Multimedia Appendix 2.

Study Setting

The study is based at the Murdoch Children's Research Institute (MCRI) at the Royal Children's Hospital in Parkville, Melbourne, VIC.

Eligibility Criteria

Participants were eligible if they did not meet the exclusion criteria and could attend a Saturday workshop at the Royal Children's Hospital between weeks 26 and 29 of gestation.

Exclusion Criteria

To ensure practicality, participants were excluded if they were aged under 18 years, not in control of their diet (including choice of foods purchased and meals eaten), were uncomfortable communicating in English, or resided further than 1 hour's travel from the Hospital. To ensure suitability of the dietary intervention, participants were excluded if they had a clinically diagnosed bowel condition or were on a medically advised exclusion or restriction diet. To assess intervention efficacy, participants needed to be free of conditions that may alter their gut microbiota. Hence, participants must not have had any of the following: a body mass index of 30 or greater; diabetes mellitus (type 1, 2, or gestational diabetes); a clinical diagnosis of a current mental illness (including major depression, dysthymia, anxiety disorder, social phobia, posttraumatic stress disorder, obsessive compulsive disorder, panic disorder, an eating disorder [anorexia, bulimia, and binge-eating disorder]), psychotic disorder (schizophrenia), substance use disorder, autism disorder, attention deficit hyperactivity disorder, attention deficit disorder; or used antibiotics or probiotic supplements in the previous month; or regularly use illicit drugs.

Sample Size and Power

The study was powered to detect a between-group difference in alpha diversity (Shannon index) in infants. At design time in 2015, very few studies reported infant alpha diversity measured at 4 weeks, and no studies that we are aware of have ever reported differences in infant alpha diversity as a function of a maternal dietary intervention; thus, it was difficult to estimate an expected change. Instead, a clinically relevant difference in Shannon index was determined based upon the small number of case-control studies reporting differences between the Shannon index of healthy 4-week old infants to those with health problems (such as allergy) [2,4,27]. Across these studies, the

mean between-group difference in Shannon index ranged between 0.2 and 0.3. Standard deviations were derived for each group ranging between 0.2 and 0.5, with 0.4 being most common. On the basis of these data, the sample size was calculated using the power.*t* test function of the R *stats* package (R Core Team, version 3.2.0). A sample of 80 mothers would provide 80% power to detect a difference in Shannon index of at least 0.25, assuming a standard deviation of 0.4 and a 2-sided type I error of 0.05. Therefore, 90 pregnant women would be recruited to participate, this permitted a loss to follow-up of 10 participants (12.5%).

Recruitment

Melbourne-based women were recruited online or within the community (obstetric clinics, doctor's surgeries, maternal and child health centers, childcare, playgroups, toy libraries, shopping centers, physiotherapy centers, sports centers, and radio). Online recruitment strategies included pregnancy forums, twitter, and paid Facebook advertisements that targeted Melbourne-based women aged between 18 and 40 years who met Facebook pregnancy-related demographic characteristics.

Randomization

The randomization process used a concealed 1:1 group allocation ratio with randomly permuted block sizes to ensure allocation was unpredictable. External personnel prepared the randomization schedule and applied it to the Research Electronic Data Capture (REDCap) randomization module [28]. The study administrator used REDCap to randomly allocate each participant. After allocation, blinding was no longer possible because the team had to book study visits or a workshop.

Participation

As a gesture of appreciation, participants received an Aus $20 grocery store gift voucher at the initial study visit. In recognition of effort, completed participants entered a raffle to win an Apple iPad, this was drawn at the end of the study. When the study results are known, participants will receive a summary of results and an invitation to attend a presentation.

Intervention

The objectives of the dietary intervention were that participants become educated, motivated, empowered, and equipped with the skills and self-efficacy to make long-term dietary change targeting the gut microbiota. The gut microbiota were targeted as the intervention's change mechanism, and the target behavior was *eating for the gut microbiota*. We expected that the intervention would be feasible and accepted because when asked about support preferences, pregnant women wanted nutrition education, preferably in person and individually tailored [18,29].

Intervention Procedures

Participants attended a dietary workshop between gestation weeks 26 and 29. Participants devised and agreed upon 3 personalized dietary goals, and they received 2 support calls to encourage adherence. Intervention procedures are detailed in Multimedia Appendix 3. For intervention fidelity, each workshop and support call followed a predefined facilitator script to ensure that all participants received the same information.

Dietary Recommendations

The intervention aimed to align participants' diets to the Australian Dietary Guidelines [25], and increase intakes of fibrous plant-based foods, while reducing intakes of highly refined and processed foods. Common probiotic species (*Lactobacillus* and *Bifidobacterium*) are reported to be safe during pregnancy [30], and perinatal probiotic supplementation may increase Bifidobacterial species in infants [11]. The intervention took a sustainable, *whole of diet approach* where prebiotic- and probiotic-containing food sources were recommended to participants instead of using supplements. This *synbiotic* combination of prebiotic and probiotic foods may help to promote the growth of probiotic species [31].

Educational Design

The educational design used the theory of constructive alignment [32], which argues that alignment among intended learning outcomes, learning activities, and assessment is crucial for learning. Clear learning outcomes were developed for the workshop (Multimedia Appendix 4) using the Structure of Observed Learning Outcomes taxonomy [33], which allows targeting particular levels of functioning with respect to knowledge. Learning activities were designed to provide opportunities for learners to practice the particular learning outcomes; this aligns with constructive alignment's focus on what learners do rather than on what educators do. Participants engaged in active learning tasks like problem solving, which have been shown to be more effective for learning than transmissive or *lecture* style teaching [34]. At an educational psychology level, learning activities were designed with consideration of cognitive load theory [35] to manage the demands on participants' working memory; this was deployed through chunking content, provision of reference materials, and careful use of different media. The workshop focused on developing participants' ability to make judgments about their diet quality. The ability to self-assess is crucial for long-term retention and application of knowledge beyond the workshop [36], as participants need to be able to judge the quality of their diet to improve it. An expert in educational design and pedagogy reviewed the workshop materials. The logic model in Multimedia Appendix 4 details how the educational design, monitoring, feedback activities, and BCTs were used in the intervention.

Behavior Change Techniques

To support adherence, the intervention used BCTs [21]. Behavior change is an effective method for supporting dietary adherence in community-based interventions [37-39], including among pregnant populations [40]. Successful dietary BCTs include social support [37,38], information [40], instruction [39,40], self-monitoring [39,40], self-efficacy [38], goal-setting [37,39], goal review [39], relapse prevention techniques [39], motivational interviewing [39,40], feedback provision [39], and rewards (if goals are met) [40]. Descriptions of the intervention's use of Michie et al's BCTs [21] are available in Multimedia Appendices 3 and 4.

Control Group

Treatment as usual was used as an active control condition. Participants continued receiving dietary advice from a health care provider who was managing their pregnancy. The rationale for using treatment as usual was to be able to compare the intervention against standard treatment [41]. In addition, provision of a different treatment as an active control may have introduced factors that could have altered the gut microbiota or bias the results.

Participants from both groups reported on the dietary advice that they received from their health care provider. Both groups also reported on their dietary intake, including prebiotic and probiotic foods, and dietary supplements. All nonwithdrawn participants received the intervention materials in written form upon study closure after sample and data collection closed.

Data and Sample Collection

Data were collected at 4 time points: gestation week 26, 31, 36, and 4 weeks after birth (follow-up), as detailed in Table 1. Data collection included demographic, physical health and medications, mental health and social support, diet, lifestyle, and evaluative feedback. A probiotic food and drink questionnaire was administered at all time points for the intervention group, but only at baseline and follow-up for the control group to prevent the control group from becoming aware or prompted to increase intake of probiotic foods.

The study team were trained to collect baseline and follow-up anthropometrics and biological samples. Biological samples were collected as outlined in Table 2. Participants collected a baseline stool sample during gestation week 26, and a follow-up sample from themselves and their infant 4 weeks after birth. Stool samples were stored in the domestic freezer and transported on ice to the study visit scheduled during week 26 of gestation (or before week 29). The study team collected the follow-up samples during a home visit. Samples were transported to long-term storage (−80°C) on dry ice. At the conclusion of the study, stool samples were couriered on dry ice to the Australian Genomic Research Facility (AGRF) for DNA extraction and 16S rRNA sequencing. The V3-V4 hypervariable region of the 16S rRNA gene was amplified using a forward primer, 341F, 5’-CCTAYGGGRBGCASCAG-3’ and reverse primer, 806R, 5'-GGACTACNNGGGTATCTAAT-3'. Polymerase chain reaction amplicons were generated from approximately 100 ng of extracted DNA, and purified amplicons were sequenced using Illumina MiSeq, in accordance with the manufacturer specification and AGRF protocols.

Table 1. Data collection schedule.

Measurement/instrument	Baseline (gestation week 26; mother)	Progress (gestation weeks 31 and 36; mother)	Follow-up (4 weeks postpartum)	
			Mother	Infant
Demographics				
Demographics, socioeconomic status, ethnicity, household composition, and pets	✓	—[a]	—	—
Physical health				
Medical health	✓	✓	✓	✓
Medication and supplement use	✓	✓	✓	✓
Oral health	✓	—	✓	—
ROME III Diagnostic Questionnaire for Adult Functional Gastrointestinal Disorders	✓	—	✓	—
Childbirth details	—	—	✓	
Anthropometrics: body mass index, weight, height	✓	—	✓	✓
Head circumference	—	—	✓	✓
Maternal psychological well-being and relationships				
The Edinburgh Postnatal Depression Scale [42]	✓	—	✓	—
Depression Anxiety and Stress Scale-21 [43]	✓	✓	✓	—
Perceived stress scale [44]	✓	—	✓	—
Big-5 personality scale [45]	✓	—	—	—
Multidimensional scale of perceived social support [46]	✓	—	✓	—
Nature relatedness scale [47]	✓	—	✓	—
Diet				
Dietary Questionnaire for Epidemiological Studies (Version 2) [24]	✓	—	✓	—
Simplified Dietary Questionnaire [26] (modified)	✓	✓	✓	—
Probiotic Food and Drink Questionnaire	✓	✓[b]	✓	
Infant diet	—	—	—	✓
Lifestyle				
International Physical Activity Questionnaire [48]	✓	—	✓	—
Smoking	✓	—	✓	—
Process evaluation				
Workshop evaluation	—	✓[b]	—	—
Study evaluation	—	—	✓	—
General self-efficacy scale [49]	✓	—	✓	—
Motivation and readiness to change [50]	✓	✓	✓	—
Intervention personal goals	—	✓[b]	—	—

[a]Not collected.

[b]Intervention group only.

Table 2. Biological sample collection schedule.

Measurement	Baseline (gestation week 26; mother)	Follow-up (4 weeks postpartum)	
		Mother	Infant
Microbiota and metabolites			
Stool sample	✓	✓	✓
Stress and inflammatory markers			
Saliva	✓	✓	—
Guthrie spot	—[a]	—	✓
Epigenetic regulation			
Buccal cells	✓	✓	✓

[a]Not collected.

Data Management and Access

Questionnaires were administered electronically to participants through REDCap [28], which is hosted on secure servers at MCRI. Information is kept confidential through a secure password-protected system and restrictive user-access permissions. Study team access to participant information was strictly limited to the purposes of running the study, such as organizing study visits, support calls, and recording biological sample collection. For analysis, the investigators have access to the final deidentified trial dataset.

Monitoring

Being a community-based health intervention, minimal harms are foreseen. No independent bodies were developed for data monitoring or auditing trial conduct. Any adverse events would be reported to the Human Research Ethics Committees (HRECs) in accordance with the safety reporting policy of the HREC. SD, JMC, and FNJ oversaw the implementation of the study, and the HRECs of The Royal Children's Hospital and Deakin University review its progress.

Availability of Data and Materials

Data sharing is not applicable, and no data have been reported.

Statistical Methods

The study results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [51]. Analyses will be performed according to a modified intention-to-treat principle, in which participants with at least 1 valid postbaseline follow-up are included.

Primary Outcome

The infant Shannon Diversity Index (collected 4 weeks after birth) will be calculated using the phyloseq R package [52]. Normal distribution will be assessed by visually inspecting quantile-quantile plots. If data are normally distributed, then an independent student *t* test will be conducted, otherwise a Wilcoxon-Mann-Whitney U test will be conducted to determine between-group differences, where statistical significance is considered at the P<.05 level [53].

Additional Multivariable Analysis

Additional multivariate analysis will be performed to examine potential effect modifiers (sample storage duration, birth mode, antibiotic exposure, gestational age, and mode of feeding) using Kraemer et al's [54] approach as a guideline.

Secondary Outcomes

Gut Microbiota

Infant stool alpha diversity will be further analyzed using 4 other measures (Inverse Simpson, Chao1, phylogenic diversity, and observed species) using the same methods described for the primary outcome. All 5 alpha diversity measures will be analyzed for mothers adjusting for baseline measures. Further analyses will examine potential effect modification for storage duration, baseline, antibiotic, and medication use in accordance with Kraemer et al [54]. Between-group differences in the relative abundance of genus *Prevotella* will be analyzed using the same methods described for the primary outcome for infants and a baseline-adjusted method for the mothers.

A total of 2 beta diversity metrics will be calculated (Generalized UniFrac distances [55] and Bray-Curtis dissimilarity.) Group-based separation will be visually inspected using principal coordinates analysis and constrained ordination plots of these beta diversity metrics. Further plots will be created to inspect separation based on potential effect modifiers: mode of birth, antibiotics, sample collection week, and mode of feeding. Permutational multivariate analysis of variance (PERMANOVA) [56] with 999 permutations will be used on the beta diversity metrics to determine the statistical significance of group-based separation. In a secondary analysis, these PERMANOVA models will test for the aforementioned potential effect modifiers. Differential abundance testing with a false discovery rate correction will be performed to explore OTUs that are different between groups. The appropriate transformation and test will be determined in accordance with Weiss et al once library size is known [57]. For significant outcomes, the role of dietary change or probiotic or prebiotic supplementation in potentially mediating microbial outcomes will be examined.

Intervention Efficacy and Dietary Intake

Linear mixed model analyses using the generalized estimating equation (GEE) technique will be used to evaluate between-group baseline-adjusted mean differences, accounting for within participants autocorrelations across multiple time-points, for the 14 DGI-13 long-term diet measures [23], 6 macronutrient measures [24], and the 13 SDQ short-term diet measures [26]. All tests will be 2-sided, and statistical significance is considered at a P value <.05. No correction for multiple comparison will be implemented for these outcome analyses as these comparisons are *a priori* research questions with specified alternative hypotheses. Time trends in short-term diet quality and intakes of prebiotic and probiotic foods are evaluated from baseline to before birth, and baseline to after birth. For significant outcomes, the role of motivation or mental well-being in potentially mediating any impact of the intervention on dietary intake will be examined.

Analysis plans for all nonmicrobial secondary outcome measures including SCFAs, inflammation, epigenetic regulation, behavior change, well-being, feasibility, and acceptance are detailed in Multimedia Appendix 5.

Ethics Approval and Consent to Participate

This study was approved by the Royal Children's Hospital Human Ethics Committee on the December 17, 2015 (HREC 35200), and Deakin University Human Ethics Committee on the February 16, 2016 (DUHREC 2016-036). Current protocol: Version 15, November 17, 2017. Protocol modifications will be detailed in subsequent papers.

Participants provided written informed consent and may have optionally consented to (1) be contacted about future related research and (2) to have data and samples used for future ethically approved research.

Results

The study is ongoing as results are yet to be written. The first participant was enrolled on July 28, 2016, and the final follow-up assessment was completed on October 11, 2017.

Discussion

This is the first study to test the efficacy of an educational dietary intervention in influencing the gut microbiota of mothers and infants. This study has many strengths, including its RCT design, strict inclusion and exclusion criteria, robust intervention design, wide range of data and bio-specimen collection, and an *a priori* analysis plan.

The intervention design was particularly important because when studies depend on nutrition education to test the effects of dietary change, it can be difficult to determine whether any null results are because of participants not learning, or because of the hypothesized dietary mechanism. If participants do not learn, then they cannot be expected to change their dietary behavior. Thus, study validity is dependent, to an extent, on the quality of the nutrition education. A previous systematic review found that the use of theory was associated with nutrition education intervention success [58]; however, we draw a distinction between dominant high-level theories used in those studies (eg, social cognitive theory) and the lower level educational design theories used in this study. Higher level theories provide less of an evidence base for practical matters, such as the translation of study objectives to intended learning outcomes, mapping outcomes to specific activities, and the selection of appropriate media or designing PowerPoint slides. Lower level educational design considerations are important because they are influential in how well participants learn. The intervention design is a key strength of this study with its clear alignment among the target behaviors, intended learning outcomes, learning activities, BCTs, and participant self-monitoring.

Regardless of a participant's baseline diet quality, we expect that the intervention will be effective in increasing average intakes of fiber, and prebiotic, and probiotic foods. These foods were specifically targeted in the intervention, while the control group was unaware of the interest in these prebiotic and probiotic foods. We anticipate that the diversity of the prenatal gut microbiota is stable and will respond to this dietary change. DiGiulio et al demonstrate that stool alpha diversity is stable from week-to-week during pregnancy and the postpartum period [59]. Elsewhere, Koren et al report that there is significant instability during pregnancy [60]. However, samples were only collected at 3 time points (not weekly), and critically, a subset of participants may have been involved in a dietary intervention consuming probiotics [61]. In nonpregnant adults, gut microbiota respond to short-term dietary intake within 24 hours [62,63]. Hence, dietary change needed to be sustained through to follow-up when the final stool sample was collected. We addressed this in our intervention design through the use of BCTs [21,39], and during the last support call (before birth), we discussed how each participant plans to sustain their dietary goals after birth (Multimedia Appendix 3).

The study is powered to test for an overall effect of the intervention. The overall intervention effect will be unbiased on the basis that the study has an RCT design, where we expect that potential effect modifiers or confounders (both measured and more importantly unmeasured) will be balanced out between groups. The study will not be underpowered unless there is strong heterogeneity because of a potential effect modifier. Based upon the population rates, we expect the majority of births to be vaginal, and majority of infants will be breast fed (67% vaginal birth, 33% cesarean [64], with 74.6% breastfeeding at 1 month [65]). The study may not have power to detect the role of effect modifiers, but this was not the main study aim. Our sample size calculation was based upon an estimated standard deviation of 0.4, we recently reassessed the accuracy of this estimate using recently available 16S data for 144 4-week old infants from the INFANTMET cohort [66]. We analyzed these data and arrived at a standard deviation of 0.317; this is lower than our original estimate, indicating that our sample size calculation may be conservative.

Given that this is the first study to measure changes in Shannon index of 4-week old infants as a function of a perinatal dietary intervention, we could not base the effect size upon established dietary intervention data. Instead, we used a clinically meaningful difference in Shannon index, by basing the

calculation on detecting a difference in Shannon index as small as 0.25. This represents the mean between-group difference in Shannon index between allergy case and controls at 4 weeks across 3 studies [2,4,27]. If this study is efficacious, then our use of a clinically meaningful difference may assist in interpreting and translating the results. We urgently need data from human experimental studies (such as this study) to inform similar interventions. Without pre-existing data, it is difficult to estimate whether the selected effect size is too optimistic. Importantly, this study will generate the data needed to inform power calculations for future perinatal dietary intervention studies.

Conclusions

To our knowledge, there are currently no human trials testing the hypothesis that the diversity and composition of the infant gut microbiota is modifiable through the perinatal diet. Animal studies implicate poor maternal diets (high intakes of fat or low fiber) in the disturbance of gut microbiota in offspring [8,9]. Experimental studies are needed to determine whether this holds in humans. This is particularly important because diet quality during pregnancy appears to be poor, with many women failing to meet recommendations for fiber and energy and exceeding the recommendation for fat intake [17]. Data arising from this study may inform future interventions aiming to target the composition of the gut microbiota in early life. The results of this study may also be used to inform clinical and public health recommendations supporting the gut microbiota in early life.

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Authors' Contributions

All authors meet the criteria for authorship. SLD is the principal investigator for the study responsible for: study design, intervention design, obtaining ethical review, and study management, implementation, intervention delivery, and statistical analyses. FNJ is responsible for initial study conception, input into study design, supervision, and study oversight. PD advised on and reviewed the education design. FNJ reviewed the dietary workshop. JMC provided oversight and sample collection and storage procedures. MM reviewed and contributed to statistical methods. FNJ, JMC, GC, MLKT, MM, and PD provided expert feedback. SLD drafted this manuscript, and all authors provided input and revision. All authors approved the final manuscript.

Conflicts of Interest

The authors' competing interests are unrelated to this study. APC Microbiome Ireland is a research center funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan (grant no 12/RC/2273). GC is currently in receipt of research funding from the Irish Health Research Board (Grant number ILP-POR-2017-013) and by the US Airforce Office of Scientific Research (Grant number FA9550-17-1-006). GC has previously received funding from the Brain and Behavior Research Institute. APC Microbiome Ireland collaborates with a number of industry partners including Dupont Nutrition Biosciences APS, Cremo SA, Alkermes Inc, 4D Pharma PLC, Mead Johnson Nutrition, Nutricia Danone and Suntory Wellness. GC has spoken at meetings sponsored by food and pharmaceutical companies including Janssen Ireland and Probi. This neither influenced nor constrained the content of this publication. MLKT is a past member of the Nestle Nutrition Institute medical advisory board; past member of Nutricia Global Scientific Advisory Board and has received speaker fees from Nestle Health Sciences, Nutricia, Abbott. FNJ has received Grant/Research support from the Brain and Behaviour Research Institute, the National Health and Medical Research Council (NHMRC), Australian Rotary Health, the Geelong Medical Research Foundation, the Ian Potter Foundation, Eli Lilly, Meat and Livestock Australia, Woolworths Limited, Fernwood Gyms, The Wilson Foundation, GMHBA and The University of Melbourne and has received speakers honoraria from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Health Ed, Network Nutrition, Angelini Farmaceutica, Eli Lilly and Metagenics. She is supported by an NHMRC Career Development Fellowship (2) (#1108125). FNJ has written two books for commercial publication and has a personal belief that good diet quality is important for mental and brain health.

Multimedia Appendix 1
Secondary hypotheses.

[PDF File (Adobe PDF File), 30 KB - resprot_v8i10e14771_app1.pdf]

Multimedia Appendix 2
Secondary outcome measures.
[PDF File (Adobe PDF File), 38 KB - resprot_v8i10e14771_app1.pdf]

Multimedia Appendix 3
Intervention procedures and behavior change technique usage.
[PDF File (Adobe PDF File), 47 KB - resprot_v8i10e14771_app3.pdf]

Multimedia Appendix 4
Intervention logic model.
[PDF File (Adobe PDF File), 101 KB - resprot_v8i10e14771_app4.pdf]

Multimedia Appendix 5
Statistical methods for secondary outcomes.
[PDF File (Adobe PDF File), 41 KB - resprot_v8i10e14771_app5.pdf]

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Abbreviations

BCT: behavior change techniques
DGI-13: Dietary Guideline Index 2013
DQES: Dietary Questionnaire for Epidemiological Studies
HPHK: healthy parents, healthy kids
kJ: kilojoules
MCRI: Murdoch Children's Research Institute
OTU: operational taxonomic units
PERMANOVA: permutational multivariate analysis of variance
RCT: randomized controlled trial
REDCap: research electronic data capture
SCFA: short chain fatty acid
SDQ: Simplified Dietary Questionnaire

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Protocol

Improving Transplant Medication Safety Through a Technology and Pharmacist Intervention (ISTEP): Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Medication errors, adverse drug events, and nonadherence lead to increased health care utilization and increased risk of adverse clinical outcomes, including graft loss, in solid organ transplant recipients. Veterans living with organ transplants represent a population that is at substantial risk for medication safety events and fragmented care coordination issues. To improve medication safety and long-term clinical outcomes in veteran transplant patients, interventions should address interorganizational system failures and provider-level and patient-level factors.

Objective: This study aims to measure the clinical and economic effectiveness of a pharmacist-led, technology-enabled intervention, compared with usual care, in veteran organ transplant recipients.

Methods: This is a 24-month prospective, parallel-arm, cluster-randomized, controlled multicenter study. The pharmacist-led intervention uses an innovative dashboard system to improve medication safety and health outcomes, compared with usual posttransplant care. Pharmacists at 10 study sites will be consented into this study before undergoing randomization, and 5 sites will then be randomized to each study arm. Approximately, 1600 veteran transplant patients will be included in the assessment of the primary outcome across the 10 sites.

Results: This study is ongoing. Institutional review board approval was received in October 2018 and the study opened in March 2019. To date there are no findings from this study, as the delivery of the intervention is scheduled to occur over a 24-month period. The first results are expected to be submitted for publication in August 2021.

Conclusions: With this report, we describe the study design, methods, and outcome measures that will be used in this ongoing clinical trial. Successful completion of the Improving Transplant Medication Safety through a Technology and Pharmacist Intervention study will provide empirical evidence of the effectiveness of a feasible and scalable technology-enabled intervention on improving medication safety and costs.

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KEYWORDS

transplant; adherence; medication adherence; medication errors

Introduction

Background

Over the past 20 years, the use of contemporary immunosuppression has reduced the risk of rejection by more than 80%, but long-term allograft survival remains suboptimal [1,2]. Current immunosuppressants are highly effective but carry the burdens of considerable toxicities, multiple drug interactions, and complex regimens. Drug-related problems, which encompass medication errors, nonadherence, and adverse drug events, are a predominant cause of deleterious clinical outcomes in solid organ transplant recipients—most notably, graft loss [3-6]. Our previous research, as well as studies from other groups, demonstrates that drug-related problems occur in two-thirds of transplant recipients, leading to potentially avoidable hospitalizations in 1 in 8 recipients; those that develop medication errors are at considerably higher risk of graft loss [6-9].

Previous research has demonstrated that transplant recipients are burdened with numerous risk factors for the development of medication safety events. These include taking more than 10 medications concomitantly with more than 30 doses ingested per day, being prescribed narrow therapeutic index medications that are prone to drug interactions, taking chronic immunosuppressants with known debilitating side effects, and having frequent dosage adjustments. In addition, long-term ambulatory transplant recipients usually receive care across multiple health care organizations; thus, fragmented care, omissions, duplications, and discrepancies in medication regimens are common among these patients. We have also established this as a major issue facing veteran transplant recipients. Veteran transplant recipients who receive care from a transplant center outside their primary Veterans Health Administration (VHA) location are particularly at risk for these types of errors [6,7,9-11].

There is widespread consensus that the use of multiple sources of health care may hinder effective care coordination and result in care fragmentation and duplication of services, leading to poorer outcomes and higher costs [12-14]. Millions of veterans are eligible for health care services covered by their VA benefits and other insurance, such as Medicare or a private health care plan. Although the VA Health Care System offers comprehensive care, many receive health care services at both VHA and non-VHA facilities. Patients with ongoing care in both VA and non-VA settings can be described as receiving dual care and are often referred to as *dual users* [15,16]. Although the use of dual health care systems increases access and care options for veterans, dual use also increases the potential for care to be uncoordinated or fragmented[17,18]. Previous work on veterans who use both VHA and Medicare inpatient or outpatient services has found that dual (vs single) system users experienced higher rates of rehospitalization after heart failure or acute stroke and increases in mortality risk[19-22]. Among veterans with diabetes, 1 study demonstrated that dual users with diabetes were significantly more likely than VA-only users to be overtested for both hemoglobin A_{1c} and microalbuminuria, and another reported evidence of substantial overuse of glucose test strips among dual health care system users [23,24].

Veteran transplant recipients are embedded within highly complex interfacility systems of care such that medication safety monitoring and care coordination in the ambulatory care setting are often fragmented and suboptimal. Our previous research has demonstrated that nearly two-thirds of veteran transplant recipients are dual users, with 62% having multiple providers managing the same conditions. This leads to a significant number of duplications and omissions in care. Medication discrepancies between systems are nearly universal as well. Thus, provider-level and system-level issues represent substantial reinforcing and enabling factors driving medication safety events in veteran transplant recipients [11].

Early recognition of adverse drug events in transplant recipients will likely help prevent downstream clinical sequelae, including nonadherence and irreversible immunosuppressant toxicities. Research demonstrates that clinical pharmacists have the unique education and training to both identify these events early while also developing strategies to mitigate or resolve the associated sequelae [25-31].

The Improving Transplant Medication Safety through a Technology and Pharmacist Intervention (ISTEP) study seeks to improve medication safety for high-risk veterans using 2 innovative components: the utilization of a dashboard monitoring system to conduct automated surveillance for immunosuppressant safety issues and alert pharmacists when such a potential issue arises coupled with a pharmacist-led intervention to improve the management and coordination of immunosuppression therapy. The ISTEP dashboard is an expanded version of a preliminary Web-based medication safety dashboard currently used within Veterans Integrated Services Networks (VISNs) 7 and 12. Through a collaborative effort between the investigators and the Medical University of South Carolina Biomedical Informatics Center, we have expanded the dashboard to significantly improve its query and reporting capabilities. The goal of this study is to demonstrate a scalable pharmacist intervention that leverages technology and analytics to improve medication safety and clinical outcomes as well as reduced utilization at lower costs for veteran organ transplant recipients.

Objectives

The complexities and toxicities associated with immunosuppressive medication regimens and fragmentation of care across multiple health organizations place veteran organ transplant recipients at high risk of developing medication safety issues, which can lead to hospitalization, increased health care expenditures, and ultimately graft loss. Supported by previous research [32,33], the use of a technology-enabled, pharmacist-led intervention provides a promising and innovative

approach to improve medication safety and reduce drug-related problems in veteran solid organ transplant recipients.

The study will measure the clinical and economic effectiveness of a pharmacist-led intervention that uses an innovative dashboard monitoring system that alerts pharmacists when potential drug safety issues arise to improve medication safety and health outcomes, compared with usual posttransplant care.

The primary objective of the study is to measure the effectiveness of a pharmacist-led, technology-enabled intervention on reducing the rate of hospitalizations and emergency room (ER) visits in veteran organ transplant recipients, compared with usual care. Secondary objectives include measuring the effectiveness of the intervention on reducing health care costs (compared between the intervention and control groups) and assessing the functionality and efficiency of the dashboard system. The goal of this research is to demonstrate the effectiveness of a feasible and scalable technology-enabled intervention on improving medication safety and health care costs.

Methods

Study Design

ISTEP is a 24-month prospective, parallel-arm, cluster-randomized, controlled multicenter study involving 10 study sites (5 sites for each study arm). Across the 10 VA health care systems, approximately 1600 veterans will be evaluated between the intervention and control groups for the primary outcome. This study has been approved by the VA central institutional review board.

Recruitment, Screening, and Enrollment Procedures

A pragmatic clinical trial, the ISTEP study aims to test the effectiveness of the intervention in routine clinical practice using broadly inclusive criteria for study participation. Veteran patients will be included in this study if they are solid organ transplant (eg, kidney, liver, pancreas, heart, or lung) recipients who have active outpatient prescriptions for immunosuppressant medications at 1 of the 10 participating VA health care organizations.

As this is a cluster-randomized study, randomization will occur at the site level rather than the patient level. The cluster-randomized design of this study was chosen for a number of important reasons. A cluster-randomized study design allows investigators to test a promising intervention against a similar control group with respect to patient constitution and time. Randomization at the patient level, as opposed to the site, would not be feasible, as there would be a high probability of cross-contamination based on the intervention proposed and the technology component, which uses site-specific population surveillance. Finally, randomization at the patient level would have required individual patient-level consent, which would have limited our ability to have adequate power to test the outcome of interest in the 3-year study period.

Informed written consent will be obtained from the participating pharmacist(s) at each study site. Following this, each site will be randomized through computerized random number generation to standard care or standard care plus the pharmacist-led, technology-enabled intervention. To ensure a roughly equal number of patients between the 2 comparison groups, randomization will be stratified by each site's estimated number of veteran organ transplant recipients (<125 vs ≥125 active patients). After randomization, each participating pharmacist will be informed of their assigned group. Those in the intervention arm will be trained on the dashboard system's functionality using the dashboard and delivering the intervention. Those in the usual care group will continue to provide the same level of care they are currently providing as part of their normal day-to-day activities and job functions.

Eligibility

Inclusion Criteria

Veteran organ transplant recipients will be identified using International Classification of Diseases, Ninth Revision and Tenth Revision, codes from the VA electronic health record. Patients must have an active code stating they are a recipient of an organ transplant. Patients must be receiving at least one antirejection medication dispensed by the VA site. These medications include tacrolimus, cyclosporine, azathioprine, mycophenolate, sirolimus, everolimus, or belatacept.

Exclusion Criteria

As a pragmatic clinical trial, exclusion criteria were kept to a minimum. All veterans meeting inclusion criteria will be monitored by the dashboard and will be included in the outcomes assessment. Patients may enter or exit the study in a rolling manner, which will be accounted for during analysis.

Intervention

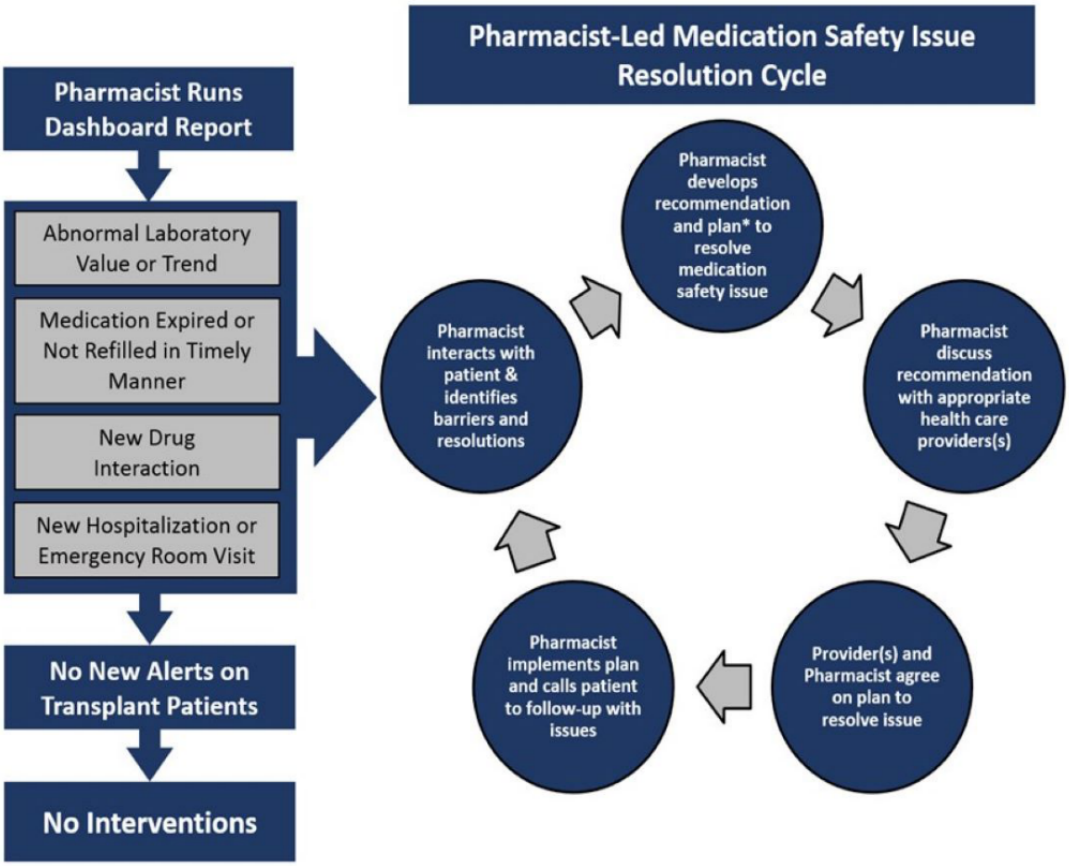
The sites randomized to the intervention arm will continue to use the current standard of care procedures within their sites while also using the dashboard system daily to identify patients with potential medication safety issues. Usual care for veteran organ transplant recipients across the 10 study sites is not standardized but generally includes the following: at most sites, nurse coordinators and/or midlevel practitioners are responsible for general transplant patient oversight, including ensuring laboratory assessments are scheduled/reviewed and medication regimens are accurate and up to date. However, large patient numbers and workload constraints preclude these health care professionals from prospective detailed daily monitoring of patients. In addition, during this long-term ambulatory phase of care for transplant patients, pharmacists usually act as consultants and are only involved in direct patient care if an issue arises, and the nurse or provider engages the pharmacist for assistance. Within usual follow-up care, pharmacists do not conduct routine daily surveillance of all transplant patients.

The intervention consists of increased review of patients by a pharmacist and increased scrutiny of patients' medication regimens and laboratory values using a dashboard surveillance system. The dashboard will be updated at approximately 7 am every day. Participating pharmacists randomized to the intervention arm will be expected to check the dashboard for alerts at a minimum of 3 days per week. The 4 primary medication safety issues the intervention pharmacists will be

alerted to and address are laboratory abnormalities, medication nonadherence, drug interactions, and medication coordination or communication issues. For each of the laboratory values that will be monitored and reported in the dashboard, a detailed algorithm will be provided delineating how to address the issue.

The pharmacist will serve as a patient navigator, intervening to resolve the medication safety issue. Once the pharmacist validates that the dashboard alert is a relevant issue, they will develop a management plan using the study's developed protocols (Figure 1). Pharmacists will then discuss the recommendations with the relevant providers (as necessary) to agree on a plan; the pharmacist will then be responsible for implementing the plan. One example alert may be for hypomagnesemia, as this is a well-known adverse effect of calcineurin inhibitors [34]. Strategies the pharmacist may implement to address this include dietary interventions and supplementation. Other relevant alerts and corresponding interventions will be addressing out of range drug levels. These interventions may include ensuring the patient is taking the correct dose, ensuring the level is a true trough value, checking for new drug interactions, and adjusting the dose when necessary. The pharmacists will be alerted when a patient fails to refill an immunosuppressant medication in a timely manner, perhaps indicating nonadherence. When medication nonadherence is identified as a potential issue, the pharmacist will then assess this information and call the patient to address this issue. Strategies to address deliberate nonadherence include removing perceived or actual barriers, using motivational interviewing, and addressing side effects and cost concerns. For unintentional nonadherence, pharmacists can implement trigger reminder strategies, simplify regimens, and re-educate. Within drug interaction alerts, the intervention will focus on reducing the impact of these through changing of regimens (when appropriate), educating patients or providers, and increased monitoring and surveillance [35]. Alerts for medication coordination issues will encompass discharges from the ER/hospital and missed laboratory assessments. The intervention pharmacist will ensure accurate and safe medication regimens through medication reconciliation and improved medication safety surveillance through the scheduling and follow-up of laboratory assessments [26].

Figure 1. Schematic representation of the process the pharmacist will use to identify, manage, and resolve potential medication safety issues.



Dashboard System Specifications

The technology component of this intervention consists of the use of a dashboard system that performs population-level surveillance of organ transplant recipients and identifies those with potential drug-related problems. The dashboard system was built using Microsoft Structured Query Language (SQL) Server Management Studio, using the Python programming language and a local Web browser for the user interface. We have expanded the preliminary dashboard currently in use by VA VISNs 7 and 12 to improve its query and reporting capabilities. The SQL queries to identify the triggers required in the expanded application are stored in the Field Reporting

Enclave environment. The dashboard expansion will contain 4 additional immunosuppressant safety monitoring domains.

First, the system monitors for immunosuppressant nonadherence through the tracking of refill activity and expiring medications.

The dashboard will alert if a medication has not been refilled or if a medication has expired. Pharmacists will be alerted when the patient's proportion of days covered (PDC) for an immunosuppressant medication falls below 80%, meaning that they have had less than 80% of days' supply on hand over the past year, as calculated by quantity and refill dates. The dashboard also includes expanded laboratory monitoring capabilities to include monitoring for missing laboratories and laboratory values (not checked in 6-12 months, depending on the laboratory value and the immunosuppression regimen) that would indicate the development of a potential adverse drug event (immunosuppressant toxicity or ineffectiveness). The dashboard will also monitor laboratory value trajectories and alert the pharmacist of patients who have trends in key laboratory values suggesting the development of a potential adverse drug event; for example, setting a trigger such that the serum creatinine concentration has increased more than 30% since the last recorded value. Finally, the dashboard will monitor drug interactions, including newly added or discontinued drugs or changes in the dose or dosing regimen of an interacting drug would also trigger an alert (Tables 1 and 2). Validation of the dashboard was conducted before the study opening and will continue during the initial deployment by the participating pharmacists at the 5 intervention sites. If there is strong evidence to suggest that components of the dashboard are not providing clinically relevant alerts or if the ratio of alerts to actionable alerts is exceedingly high, the investigational team may decide to modify this component of the system. These process measures will serve to assess the dashboard functionality and allow for modification to improve the efficiency of the intervention.

Table 1. Specifications of the transplant medication monitoring dashboard system–laboratory thresholds and specific drug interaction that warrant review.

Monitoring variables: laboratory assessments	Absolute value thresholds	Trajectory threshold
Potassium	<3 or >5.5 mEq/L	>30% change
Bicarbonate	<18 or >30 mEq/L	>30% change
Blood urea nitrogen	>40 mg/dL	>30% increase
Creatinine	>2.5 mg/dL	>20% change
Glucose	<60 or >200 mg/dL	>30% change
Calcium	<7 or >10 mg/dL	>30% change
Magnesium	<1.0 or >2.5 mEq/L	>30% change
Phosphorus	<2.0 or >5.0 mg/dL	>30% change
White blood cell count	<3.0 or >15.0 cells/mm^3	>30% change
Hemoglobin	<8 or >15 gm/dL	>20% change
Platelets	<50 or >500 cells/mm^3	>30% change
Aspartate aminotransferase	>60 U/L	>20% increase
Total bilirubin	>1.5 mg/dL	>20% increase
Hemoglobin A_{1c}	>8%	>20% increase
Low-density lipoprotein	>130 mg/dL	>20% increase
Triglycerides	>300 mg/dL	>20% increase
Tacrolimus trough	<3 or >15 ng/mL	>20% change
Cyclosporine trough	<30 or >400 ng/mL	>20% change
Sirolimus trough	<2 or >8 ng/mL	>20% change
Everolimus trough	<2 or >8 ng/mL	>20% change

Table 2. Specifications of the transplant medication monitoring dashboard system–specific drug interaction that warrant review.

Interacting drugs	Trigger definitions
Enzyme inhibitors	
Macrolides (clarithromycin, erythromycin, telithromycin); Azoles (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole)	Initiation, discontinuation, and dose change >20%
Calcium channel blockers (diltiazem, verapamil)	Initiation, discontinuation, and dose change >20%
HIV (nafazodone, delaviridine, saquinavir, nelfinavir, indinavir, amprenavir)	Initiation, discontinuation, and dose change >20%
Miscellaneous (boceprevir, telaprevir, cimetidine, chloramphenicol, danazol)	Initiation, discontinuation, and dose change >20%
Enzyme inducers	
Antiepileptics (carbamazepine, phenytoin, phenobarbital)	Initiation, discontinuation, and dose change >20%

Data Collection

Overall, 2 general types of data will be collected: (1) operational data used for the dashboard system and (2) research data to assess the impact of the intervention on outcomes. Operational data for the dashboard will be captured through querying the national VA Corporate Data Warehouse (CDW) operational database. These data elements include diagnoses, laboratory values, medication regimens, refill histories, provider types, and health care encounters (hospitalizations and ER visits), gathered and queried daily. The research CDW system (VA Informatics and Computing Infrastructure [VINCI]) will provide data to assess outcomes occurring within the VA health care system, including hospitalizations, ER visits and costs, and mortality. CDW data will also be used to assess interventions by querying pharmacists' progress notes. To ensure encounters are captured in a comprehensive manner, we will also link the VA CDW data to Centers for Medicare and Medicaid Services (CMS) claims data and capture non-VA ER and hospitalization encounters (after study completion). The CMS data will provide non-VA health care utilization, including hospitalizations and ER visits, as well as non-VA cost estimates. Scientific Registry of Transplant Recipients data will provide all baseline donor, recipient, and transplant characteristics and clinical outcomes, including acute allograft rejection, graft loss, and death. Queries answered by intervention pharmacists will include the number of alerts received, how many were considered clinically relevant/actionable, time to conduct the intervention, and general intervention types.

Outcome Measures

The outcomes to be assessed for this study all relate to evaluating the impact of the intervention. The primary outcome measure for this study will include the overall rate of ER visits and hospitalizations, compared between the intervention and control groups, while adjusting for baseline patient, provider, and facility characteristics. As previously stated, we will link the VA CDW data to the CMS (Medicare) claims data to capture both VA and non-VA ER and hospitalization encounters and provide a more accurate assessment of health care utilization. ER visits and hospitalizations will be assessed and compared as described in the section Sample Size and Statistical Analysis Plan.

Secondary outcomes to be assessed include a cost-benefit analysis of health care costs between the intervention and control groups as well as an assessment of the dashboard system's functionality and efficacy. Overall health care costs accrued during the 24-month study and those accrued in the 24 months before study initiation will be analyzed and compared between the control and intervention groups. Cost data will be standardized using the VA Health Economics Resource Center definitions, which normalize regional differences in costs because of variation in cost of living indices. As with the primary outcome, we will also acquire and link CMS claims data to gain a comprehensive assessment of costs, including those that accrue from non-VA care (after study completion). Another secondary outcome is to assess the success of the dashboard systems expansions and utilization. To do so, we will evaluate the dashboard's functionality by measuring and reporting descriptive statistics for the alert numbers, alert relevance, time, and the actions taken with regards to the alert and the intervention magnitude. Alert and intervention information will be entered by intervention pharmacists through the dashboard interface, which will then be brought into VINCI for formal analysis. These measures will allow us to ascertain if the expanded dashboard is meeting expectations, with regards to functionality and efficiency. We will also assess the number of potential immunosuppression safety issues that occur and compare these between the 2 study arms. To do so, we will use the dashboard to provide monthly measurements of the following: percentage of patients with missing laboratory assessments; percentage of patients with alarming laboratory values without follow-up scheduled; and mean adherence to immunosuppression, based on refill timeliness and estimated using the PDC; percentage of patients with a significant drug interaction without an immunosuppressant level; and percentage of patients with hospital discharge or ED visit without follow-up scheduled. These will be measured in all patients and compared between the intervention and control groups at monthly intervals.

Sample Size and Statistical Analysis Plan

On the basis of the projected enrollment numbers, we expect to have ample power to detect a statistically significant difference between the intervention and control groups with regards to the primary aim of hospitalization and ER visit rates. We used data from a recent national study conducted between 2009 and 2012 [36]. These results demonstrated that the rate of ER visits after transplant was 1.27 per person-year, and 48% of those ER visits resulted in hospitalization. We used a conservative estimate of an intracluster correlation of 0.05 and

calculated a sample size of 1350 participants to allow us to detect a 25% relative decrease in ER visit rate and hospitalization rate with 80% power. The 25% relative improvement in rates is a conservative estimate of intervention effect, based on previous pharmacist-led initiatives the investigators have conducted [25,37]. After allowing for 15% loss to follow-up, we need a total of 1600 participants to achieve the study goals. We will stratify site randomization by estimated site sample size (<125 vs ≥125) to ensure an approximate even distribution of patients across study arms. These power calculations were conducted using a 2-sided test for counts with Poisson regression adjusting for intracluster correlation and with alpha set at .05.

For comparative statistical assessments of utilization outcomes (ER visits and hospitalizations), the 2 groups will be compared using a generalized linear mixed models (GLMM) approach [38]. This approach allows for the measurement of participants at different time points, clustering by study site, missing data under the assumption of missing at random, and time-varying or invariant covariates and can also account for the effect of correlated longitudinal measurements within participants. Outcomes that are measured longitudinally, such as graft loss and mortality, will have intervention group, time, and time-by-intervention group as primary independent variables in the model. Additional adjustment covariables will be added to the model in a second set of analyses. Covariates will include patient sociodemographics: age, sex, race, comorbidities (diabetes, hypertension, and heart failure), marital status, and education.

For the cost analysis, we will also use multivariable modeling and propensity score calibration [39]. We will assess the effect of the intervention on different sources of cost at the patient level, which include inpatient, outpatient, and pharmacy in addition to the total aggregated cost. The cost models will be estimated using log-normal or gamma models (special cases of GLMM) to examine the association of the intervention with cost, adjusting for the aforementioned patient sociodemographics, donor information, and transplant characteristics. We will estimate different models adjusting for the clinical outcomes to examine the robustness of the results.

For the assessment of the functionality of the dashboard system and the time required to complete the intervention, we will use standard descriptive statistics for these measurements, including mean (SD), median (interquartile range), proportion (percentage), and 95% CI. Missing data will be handled using several techniques, including multiple imputation and maximum likelihood [40]. Missing data mechanisms will be examined using both univariate and multivariate methods.

Results

This study is ongoing. Institutional review board approval was received in October 2018 and the study opened in March 2019. To date, there are no findings from this study, as the delivery of the intervention is scheduled to occur over a 24-month period. The first results are expected to be submitted for publication in August 2021.

Discussion

Overview

The use of the dashboard monitoring system to conduct automated near real-time surveillance for immunosuppressant safety issues and alert pharmacists when such issues arise is innovative in several ways. First, this technology leverages the currently underused enormity of data that are already embedded within the VA electronic health record system. Owing to the complexity involved in the clinical management of transplant recipients, there are substantial numbers of laboratory values and medication regimen alterations that occur within each patient. Automating the monitoring of these data to identify trends and potential patient issues allows for improved efficiency. Medication refill adherence and relevant drug interaction monitoring improve the comprehensive assessment of medication adherence and safety. Finally, monitoring for hospitalization and ER visits will allow for appropriate follow-up with the transplant teams when necessary. The use of a pharmacist-led intervention is also innovative. Although the use of clinical pharmacists to improve medication safety and outcomes is well documented, there are limited studies analyzing the effectiveness of such interventions within the transplant population, and none specifically within veteran organ transplant recipients. The limited studies that demonstrate improved medication outcomes using pharmacists' led interventions among transplant patients (a number of which are from our research group) predominantly focus on the acute perioperative hospitalization phase [25,26,41-44]. The innovative component of this proposal is the use of a pharmacist-led intervention during the longitudinal ambulatory phase, following the posttransplant surgical event. As this has now been recognized as a major contributor to medication safety issues and subsequent graft loss, studies are needed that focus efforts on improving care during this period [2,45]. Pharmacists are uniquely trained to identify medication safety issues early in their course while also capable of developing and implementing strategies to mitigate or resolve these issues and assist patients transitioning from acute to chronic phases of posttransplant care [26,28,30].

There are several challenges with health services research that have the potential to undermine the intervention. First, as this intervention seeks to improve medication safety through modifying human behaviors, there is potential for implementation issues associated with the pharmacist-led intervention; there may be actions by the patient or provider that may limit or undermine the impact of the intervention. To maintain the fidelity and consistency of the intervention, we will use structured interventions based on identified barriers, develop a detailed standard operating procedure manual for the intervention, and conduct face-to-face training with the pharmacists. Systems barriers also have the potential to limit the intervention impact. As these patients are routinely managed across multiple health care systems, both inside and outside the VA, it is important that the pharmacist-led intervention facilitates medication safety and coordination across these systems. We will train the pharmacists on the best methods to ensure optimal coordination of care for these patients and

provide tools that we currently use to improve the efficiency of outside care documentation.

Conclusions

Supported by previous research, the use of a technology-enabled, pharmacist-led intervention provides a promising and innovative approach to improve medication safety and reduce drug-related problems in veteran organ transplant recipients. Successful completion of the ISTEP study will provide empirical evidence of the effectiveness of a feasible and scalable technology-enabled intervention on improving medication safety and costs. We envision this technology can be used in the monitoring of all US transplant patients receiving care within the VA. Our long-term goal is to leverage the use of this technology to develop a VA-specific pharmacist learning collaborative to substantially improve immunosuppressant safety and outcomes within veteran organ transplant recipients.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from Health Services Research and Development.
[PDF File (Adobe PDF File)151 KB - resprot_v8i10e13821_app1.pdf]

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Abbreviations

CDW: Corporate Data Warehouse
CMS: Centers for Medicare and Medicaid Services
ER: emergency room
GLMM: generalized linear mixed models
ISTEP: Improving Transplant Medication Safety through a Technology and Pharmacist Intervention
PDC: proportion of days covered
SQL: Structured Query Language
VA: Veterans Administration
VHA: Veterans Health Administration
VINCI: Veterans Administration Informatics and Computing Infrastructure
VISN: Veterans Integrated Services Network

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Protocol

Children Immunization App (CImA) Among Syrian Refugees in Zaatari Camp, Jordan: Protocol for a Cluster Randomized Controlled Pilot Trial Intervention Study

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Abstract

Background: There are up to 19.4 million children who are still unvaccinated and face unnecessary deaths, especially among refugees. However, growing access to smartphones, among refugees, can be a leading factor to improve vaccination rates.

Objective: This study aims to determine whether a smartphone app can improve the vaccination uptake among refugees and determine the app's effectiveness in improving the documentation of vaccination records.

Methods: We developed and planned to test an app through a cluster randomized trial that will be carried out at the Zaatari refugee camp in Jordan. The study will be open to all parents who carry Android smartphones, have at least one child, and agree to participate in the study. The parents will be recruited to the study by trained volunteers at the vaccination sites around the Zaatari camp. Inclusion criteria will be the following: having at least one child of 0 to 5 years, being a local resident of the camp, and having an Android smartphone.

Results: The intervention includes an app that will allow storing Jordanian vaccination records, per child, on the parents' smartphones in Arabic and English (in an interchangeable fashion). Every record will have a set of automated reminders before the appointment of each child. The app will summarize immunization records in form of due, taken, or overdue appointments, labeled in orange, green, and red, respectively. Baseline will include the collection of our primary and secondary outcomes that are needed for the pre and postdata measurements. This includes social demographic data, any previous vaccination history, and electronic health literacy. Participants, in both study arms, will be monitored for their follow-up visits to the clinic for vaccination doses. For the study outcome measures, we will measure any differences in the uptake of vaccinations. The secondary outcome is to analyze the effect of the children immunization app on visits for follow-up doses.

Conclusions: Owing to the limited evidence of effective interventions for childhood vaccination among refugees, research in this area is greatly needed. The project will have a significant impact on the health of refugees and the public health system. In

Jordan and the Middle East, the vaccination level is low. Given the influx of refugees from the area, it is crucial to ensure a high vaccination level among the children.

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KEYWORDS

mHealth; refugees; vaccines; Jordan; Syria

Introduction

Background

Child immunization is a key component of the World Health Organization and the United Nations Children's Fund (UNICEF)'s child survival intervention package [1]. Immunizing children is an essential strategy in the primary health care services, and it is a crucial public health objective. However, internationally, there are up to 19.4 million children who are still unvaccinated and face unnecessary deaths [2], especially among refugees [3]. Owing to this, refugees from conflict-torn countries have a high risk of acquiring Vaccine Preventable Diseases (VPDs) [4], especially as half of the refugees are below 18 years [5]. In conflict-torn countries, such as Syria, the immunization systems and follow-up, along with information systems, have been weakened, and herd immunity has been compromised. Before the crisis, Syria had greater than 80% of immunization coverage [6], which reduced to below 50% during the period 2011 to 2015. The total number of measles cases also increased from 13 to 740 in late 2011 and early 2013 (approximately an increase of 57-fold in less than 12 months) [2]. Since 2011, over 3 million children, aged 0 to 5 years, have fled out of Syria, to the Middle East and Europe [7]. These children have been exposed to several risky situations on the way to their new hosting countries, including passing or living in countries with low vaccination coverage [6]. In 2017, Roberton et al reported that the vaccination rate among Syrian children was 25% and 13% in Jordan and Lebanon, respectively [8]. Therefore, they are at a high risk of acquiring VPDs. This causes a heightened risk of unnecessary outbreaks in host countries, particularly among individuals who have not been vaccinated at all or completed vaccination schedules, whether refugee or from the host population [9]. The estimated cost of hospitalization may be up to US $25,000 per case [10]. The influx of children without clear immunization records therefore creates a challenge for health providers to maintain herd immunity and vaccinate unvaccinated children [5,9,11,12]. At the same time, the vaccination rate in the hosting country is considered low, for example, in Jordan, the vaccination rate among the general population is estimated to be less than 50% [13]. Given the risk to unvaccinated children, both in the refugee populations and the general population, it is paramount that support is given to health professionals to monitor and increase the rate of vaccination among refugee children. The challenge for monitoring vaccinations among refugees is compounded by the use of the yellow vaccination cards, which are easily lost or not brought to medical consultations. The field of mobile Health (mHealth) could be used as an alternative for paper-based vaccination records, and a smartphone app could present advantages to empower parents by informing them of vaccination schedules and dates and allowing them to monitor vaccination coverage on their own. There is growing evidence on the effectiveness of smartphone technologies in supporting health care services [14], though there remain gaps in the evidence of effectiveness. Smartphones provide a novel approach to solve problems with data registration, transmission, and storage [15-18]. Currently, there are over 5.2 billion users, in low- and middle-income countries [19]. The number of purchased cell phones is expected to exceed the total number of people on earth [20]. The emergence and spread of smartphones have provided a novel approach toward improving access to health care services [17]. The advancement of technology has provided tools that can empower users [21], patients, and other populations at risk. In general, mHealth can be useful among the population and among vulnerable groups, such as refugees [22]. Refugees and other vulnerable populations use smartphones as a survival kit, to connect with their social networks and to search for information about their host countries [10]. Anecdotally, women are the main caregivers for their children, and they are active users of smartphone technologies, so they can stay in touch with their social network and seek information regarding the integration process in the hosting countries [23]. It is therefore possible to use technological innovations, such as apps, to develop appropriate tools to support both women and men refugees, as well as health care professionals involved in the delivery of urgent health services. Health technology innovation is playing a crucial role in helping refugees, in various contexts around the world, including low-, middle-, and high-income countries [24].

However, there remains a lack of well-conducted evaluations of mHealth interventions among refugee populations, particularly with respect to maternal and child health. According to our knowledge, no study has used an app to support refugees' population in recording their vaccination records and provide them an automated reminder for the vaccination visits. The purpose of this study is to develop and evaluate an mHealth intervention that helps Syrian refugees to store their immunization and health records to facilitate health information sharing at the Zaatari camp in Jordan.

Objectives

The objectives are as follows:

- To implement an integrated app intervention in collaboration with UNICEF, Ministry of Health, United Nations High Commissioner for Refugees (UNHCR), and local health service delivery partners
- To analyze the uptake of vaccination coverage (primary outcome)

- To analyze the effect of the smartphone app intervention on visits for the follow-up doses (secondary outcome)
- To conduct a thorough process evaluation of the intervention implementation

Methods

Study Setting

The study will be conducted at the Zaatari camp in Jordan (5.3 km^2), which is considered one of the largest hosting camps for refugees in Jordan and the Middle East. The camp was first opened in 2012, to host the Syrian refugees fleeing the Syrian civil war. The camp population is estimated to be hosting 80,000 refugees (approximately 15,000 persons per km^2), where approximately 20% (n=16,000) of them are under 5 years.

Study Design

This will be a cluster randomized controlled trial to evaluate the effectiveness of using an app to record the vaccination schedule, including reminders for parents, on increasing immunization coverage of Syrian children at the Zaatari refugee camp in Jordan. In March 2019, the study was announced through posters in Arabic, in the clinics. Clinicians and social workers will also inform the residents of the camps about the study. Parents interested in joining the study will be fully briefed about the study, and an informed consent form will be signed. After completing the consent form, participants (1) included in the app intervention arm (ie, children immunization app [CImA] recipients) will receive the usual care, access to the CImA app, and instructions on how to use it, in addition to updating their children vaccination card, or (2) under the usual care (control arm) of the trial, where they will receive the usual information on the benefits of vaccination, the child's yellow vaccination card will be updated, in addition to the list of appointments for the future vaccines. The vaccination sites will be enrolled on the basis of convenience, because of the security situation in the refugee camp.

Sample Size Calculation

The sample size was calculated using G*Power 3.1.9.2 for testing the effect of the intervention by McNemar test. For 1-tailed hypothesis, at a power of 80% and level of significance of 0.05, a sample of 374 children is needed to detect a clinically important change in the proportion of children who will come back for their follow-up doses after introducing the intervention (ie, odds ratio of 1.5) [25]. After adjusting to potential proportion of lost to follow-up, the estimated sample size becomes 535. The analysis will be performed using Stata Statistical Software: Release 14 (College Station, TX: StataCorp LP.).

Children Immunization App Description

The CImA app includes 5 layers: (1) health promotion messages for the benefits of vaccination, which show up on the main page; (2) storing the post of vaccination for each child, according to the vaccination schedule of the Jordan Ministry of Health, on the parents' smartphones; (3) displaying the vaccination schedule, for each child, using green, orange, and green colors, depending on vaccination status if it was received, due or overdue, respectively; (4) appointment reminder will be displayed on the users' phones at 4 different time points before the vaccination schedule (1 week, 3 days, and 1 day and the morning of the appointment). Thereafter, the user will receive 2 notifications in the coming days of the scheduled vaccine in case of missing the appointment.

Participants will be able to download the CImA app, at no cost, on their personal devices (Android only), with the help of the study staff (we will make the link invisible to public access during the study recruitment period); and (5) the stored information is in Arabic and English (in an interchangeable fashion).

Intervention

The parents will be recruited to the study by trained volunteers at the 7 local clinics, providing vaccinations, around the Zaatari camp (Figure 1). Inclusion criteria will be the following: having at least one child of 0 to 5 years, being a local resident of the camp, and having an Android smartphone that can allow CImA app installation.

The intervention includes an app that will (1) allow storing Jordanian vaccination records (Table 1), per child, on the parents' smartphones, in Arabic and English (in an interchangeable fashion), (2) have a set of automated reminders before the appointment of each child, and (3) in addition, summarize immunization records in the form of *due*, *taken*, or *overdue* appointments, labeled in orange, green, and red, respectively.

Figure 1. The distribution of districts at the Zaatari camp and the location of the health facilities providing vaccinations. A complete map for the Zaatari camp can be found at https://data2.unhcr.org/en/documents/download/55994

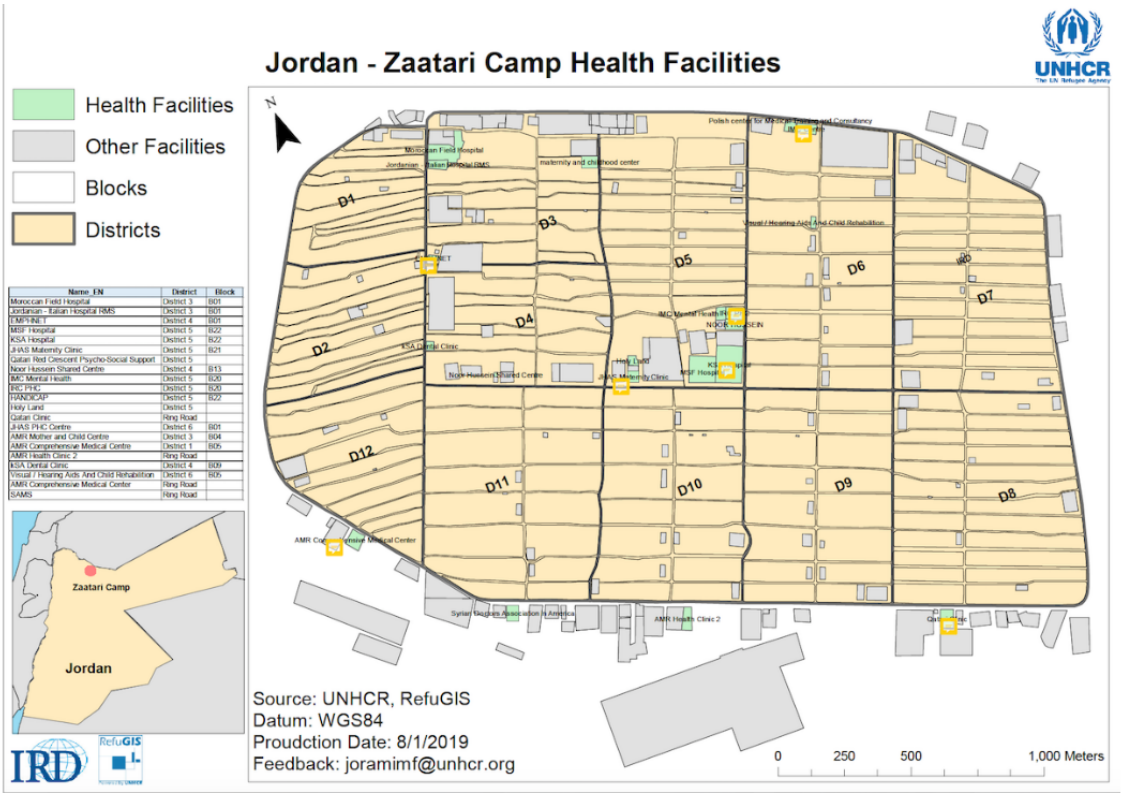

Table 1. Summary of the national vaccination schedule of the Jordan Ministry of Health.

Age	Recommended vaccines
1st contact	BCG[a]
2 months	DTaP-Hib-IPV + HBV[b]; RV[c] 1st
3 months	DTaP-Hib-IPV + HBV; RV 2nd; OPV[d]
4 months	DTaP-Hib-IPV + HBV; RV 3rd; OPV
9 months	Measles; OPV
12 months	MMR1[e]
18 months	DTP[f]; MMR2; OPV
6 years (first grade)	Td[g]; Check for MMR; OPV

[a]BCG: Bacillus Calmette–Guérin.

[b]DTaP-Hib-IPV + HBV: diphtheria, tetanus, pertussis (whooping cough), polio, *Haemophilus influenzae* type b, and hepatitis B.

[c]RV: rotavirus vaccine.

[d]OPV: oral polio vaccine.

[e]MMR: measles, mumps, and rubella.

[f]DTP: diphtheria, tetanus, and pertussis.

[g]Td: tetanus and diphtheria.

Children Immunization App Design and Security Clearance at Zaatari Camp

During the period from August to January 2019, the CImA app has been designed, developed in English and Arabic languages [26], and tested in house. In parallel to the app design and development, we have sought and obtained the security clearance from the office of the UNHCR, which has the full mandate of protecting the Zaatari camp.

Assessments

Baseline will include the collection of our primary and secondary outcomes that are needed for the pre and postdata measurements. This includes social demographic data, any previous vaccination history, and electronic health literacy [27].

Participants, in both study arms, will be monitored for their follow-up visits to the clinic for the vaccination doses. The vaccination cards of both study arms will be marked as *intervention* or *control* arm; thus, the clinic nurses will notify the field workers about the follow-up visits. For the study outcome measures, we will measure any differences in the proportion coming back on time for the follow-up vaccination visit. The secondary outcome is the utility of the CImA app.

Statistical Analysis

The analysis will be done using a set of steps. The baseline characteristics of the participants will be compared between the intervention and control groups, using independent 2-tailed *t* test for continuous variables and Chi-square test for categorical variables. Delta analysis (D%) will be used to assess the change in the vaccination rate between preintervention (t0) and postintervention (t1), contrasting this change within the intervention and control groups. This will be complemented by an effect size assessment to quantify the difference in change between the 2 groups (Cohen *d* test will be used). Hierarchical level modeling will be conducted to consider any cluster effect of the clinics (defaulters will be treated as intent-to-treat analysis in the primary outcome of the study). For the secondary outcome, survival analysis will be used to further contrast the difference in the secondary outcome (proportion of defaulters) between the intervention and comparison groups, postintervention (t1). Stata will be used for the data analysis.

Ethical Considerations

This study has been reviewed and approved by the Institutional Review Board of the Jordan University of Science and Technology (Reference# 14/112/2017, date January 14, 2018). In addition, the project proposal has been endorsed by the Minister of Health in Jordan, UNICEF-Jordan. Owing to the vulnerability of the refugees and the context of the camp, all participants will be invited to participate on a volunteer basis. Survey data will be collected at baseline followed by a survey at the end of the study. Participants will be given ID numbers, and these numbers will be stored in the app of each participant. No personal information will be stored. The research assistants will review the schedule of the app and match it against the standardized tool for the vaccination schedule of Jordan-Ministry of Health. Study participants will have their full right to cancel their participation in the study, including closing their study file. The data will be entered and stored in a secured database, using EpiData [28], and only team members will have access to it. Any reports or publications will be anonymized, and no identifying information will be included.

Benefits for the Refugees

Few studies exist in the published literature, which focus on vaccination, health information, and the needs of refugee population [29,30]. This study will determine the immunization coverage gap and attempt to reduce it among refugee population in 3 different settings and evaluate a newly designed and piloted app to replace traditional paper-based immunization and health care records, which are not an option among a traveling/mobile population [31]. This will enable refugees to keep a record of vaccinations and prevent VPDs.

Communications and Dissemination Strategy

Before the launching of the study in March 2019, we held a briefing meeting with the representatives of the clinics, social workers, and health care workers of the camp. Thereafter, bimonthly progress meetings will be conducted with the same group of representatives. This will help the development of the policy document related to immunization in the 3 countries. The results will be published in open-access peer-reviewed international scientific journals to enable wider access inside and outside these countries, especially among low- and middle-income contexts. This will benefit other countries in improving their vaccination programs, using smartphones.

Results

The study enrolment is still ongoing. We expect to complete the study by October 2019 followed by data analysis and submission of the final report by the end of 2019.

Discussion

This paper describes the study protocol for a randomized controlled trial of a smartphone app on child vaccination at one of the largest Syrian refugee camps in the world. Owing to the current gap in children vaccination coverage in Jordan, this study will provide an important preliminary insight on using a smartphone app to improve child immunization in a refugee camp, and this study will be unique in certain ways. First, according to our knowledge, this is the first cluster randomized controlled trial of a smartphone app–based intervention to support the national vaccination program. This includes the effects on the immunization coverage, follow-up visits, and the experience of both of health care staff and parents in using the app. The outcome of this study will be of high importance for the different collaborators, including UNICEF, UNHCR, and the Jordan-Ministry of Health.

Conclusions

Owing to the limited evidence of effective interventions for childhood vaccination among refugees, research in this area is greatly needed. The project will have a significant impact on the health of refugees and the public health system. In Jordan, and the Middle East, the vaccination level is low. Given the influx of refugees from the area, it is crucial to ensure a high vaccination level for the refugees, especially for children, to avoid VPDs.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from Grand Challenges Canada.
[DOCX File 77 KB - resprot_v8i10e13557_app1.docx]

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Abbreviations

CImA: children immunization app
mHealth: mobile health
UNHCR: United Nations High Commissioner for Refugees
UNICEF: United Nations Children's Fund
VPD: Vaccine Preventable Disease

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Protocol

Personalized, Web-Based, Guided Self-Help for Patients With Medically Unexplained Symptoms in Primary Care: Protocol for a Randomized Controlled Trial

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Abstract

Background: Medically unexplained symptoms (MUS) constitute a major health problem because of their high prevalence, the suffering and disability they cause, and the associated medical costs. Web-based interventions may provide an accessible and convenient tool for managing MUS. We developed a personalized, Web-based, guided self-help intervention for MUS in primary care (Grip self-help) and would compare its effectiveness with that of usual care.

Objective: This paper aims to describe the rationale, objectives, and design of a pragmatic randomized controlled trial (RCT) assessing the effectiveness of Grip self-help.

Methods: For a pragmatic multicenter RCT, 165 adult patients with mild to moderate MUS will be recruited through general practices in the Netherlands. Randomization will be performed at general practice level. Over the course of several months, patients in the intervention group will receive a personalized set of Web-based self-help exercises, targeting the unhelpful cognitions, emotions, behaviors, and social factors that are relevant to them. The intervention is guided by a general practice mental health worker. The control group will receive care-as-usual. Primary outcome is physical health-related quality of life (RAND-36 or 36-item general health survey, physical component score). Secondary outcomes include severity of physical and psychological symptoms, mental health–related quality of life, cost-effectiveness, and acceptability. Assessments will take place at baseline, end of treatment, and at 16-, 26-, and 52-week follow-ups.

Results: Recruitment started in December 2018, and enrolment is ongoing. The first results are expected to be submitted for publication in December 2021.

Conclusions: To our knowledge, this is the first study to combine the concepts of electronic health, self-help, and personalized medicine in the treatment of MUS. By improving the quality of life and reducing symptoms of patients with MUS, Grip self-help has the potential to reduce costs and conserve scarce health care resources.

Trial Registration: Dutch Trial Register NTR7390; https://www.trialregister.nl/trial/7390.

International Registered Report Identifier (IRRID): PRR1-10.2196/13738

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KEYWORDS

medically unexplained symptoms; somatoform disorders; precision medicine; eHealth; general practice

Introduction

Background

In primary care, about 50% of patients presenting with a physical complaint receive a medical diagnosis during their first visit. After extensive evaluation, approximately one-third of physical symptoms remain medically unexplained [1]. Medically unexplained symptoms (MUS) can cause significant distress and impairment for patients and are associated with high costs for society because of the resulting excess use of health care services, work absenteeism, and decreased productivity [2-4].

Although the pathophysiology of MUS is unknown, a lot has been published on factors that might trigger and maintain symptoms [5,6]. Targeting these factors, such as worries, fear, and physical inactivity, is the focus of most psychological treatments. Cognitive behavioral therapy is well studied and has shown modest improvements with regard to symptom severity and physical health–related quality of life (HRQoL) [7,8]. However, most patients with MUS are treated in primary care, and general practitioners (GPs) generally lack the time and skills to offer psychological treatment. More in general, GPs often find it difficult to treat patients with MUS [9] because of the lack of available and effective treatment options [8,10].

A recent meta-analysis has shown that self-help interventions are a promising alternative to psychological treatment for patients with MUS [11]. As self-help does not require guidance by a trained therapist, it can be easily accessible and widely available at relatively low costs, especially when offered on the Web.

Grip Self-Help

We, therefore, developed the Web-based intervention *Grip self-help*. Grip self-help is a personalized, guided self-help intervention for patients with mild to moderate MUS in primary care. On the basis of the results of Web-based questionnaires, patients receive a personalized set of Web-based self-help exercises, aimed at the unhelpful cognitions, emotions, behaviors, and social factors that are relevant to them. The intervention has an eclectic nature and contains elements of patient education, cognitive behavioral therapy, acceptance and commitment therapy, and problem-solving treatment. As far as we know, no previous research evaluated the effectiveness of such an intervention.

Objective

This paper describes the design of the randomized controlled trial (RCT) assessing the effectiveness of the Grip self-help intervention in general practice (Dutch Trial Register NTR7598). The primary objective of this RCT is to determine whether Grip self-help is superior to care-as-usual (CAU) for improving physical HRQoL at follow-up after 16 weeks in patients with mild to moderate MUS. Secondary objectives are as follows: to (1) assess the effectiveness of Grip self-help in comparison with CAU in improving severity of physical and psychological symptoms and mental HRQoL at follow-up after 16, 26, and 52 weeks, (2) investigate the cost-effectiveness of Grip self-help in comparison with CAU at follow-up after 16, 26, and 52 weeks, (3) assess acceptability of Grip self-help for patients and primary care professionals (PCPs), (4) investigate which patient characteristics predict effectiveness of Grip self-help, (5) investigate which characteristics of PCPs predict effectiveness of Grip self-help, and (6) investigate whether increased self-efficacy mediates treatment outcomes.

Methods

Study Design

This study is designed as a pragmatic multicenter randomized controlled superiority trial with 2 parallel groups and a 1:1 allocation ratio. The study protocol, intervention, participant information, and informed consent procedure have been approved by the University Medical Center Groningen Medical Ethics Committee (registration number M18.232173). The study will be conducted according to the principles of the Declaration of Helsinki (2013 version).

Participants

Patients with mild to moderate MUS will be recruited through general practices from rural as well as urban areas in the Netherlands. Of the PCPs, 2 types will be involved in this study: GPs and general practice mental health workers (GP-MHWs). GP-MHWs are nurses, psychologists, or social workers with experience in mental health care, employed by one or several general practices. PCPs will be invited to participate through local and national GP networks, social media, and Web publicity. PCPs that show interest will be informed by a letter. If desired, more detailed information can be provided by email, telephone, or during a visit to the practice. At least 1 GP and 1 GP-MHW are required to participate for a practice to take part in the study. Participating PCPs sign an informed consent form. Subsequently, the GP selects up to 15 patients with mild to moderate MUS based on the inclusion criteria described in Textbox 1. Selected patients receive a letter with information about the study. During a telephone call with one of the researchers, additional questions from interested patients will be answered and exclusion criteria (see Textbox 1) will be evaluated. When eligible patients decide to participate in the study, they will be asked to sign an informed consent form. Next, the participant will receive an email with an invitation to fill out the baseline questionnaires in a Web-based secure environment. An overview of the study procedure is provided in Figure 1.

Eligibility Criteria for Participating General Practices

Inclusion criteria: At least 1 GP and 1 GP-MHW from the practice take part in the study.

Eligibility Criteria for Participants

Textbox 1 presents the inclusion and exclusion criteria for participants.

Textbox 1. Inclusion and exclusion criteria for participants.

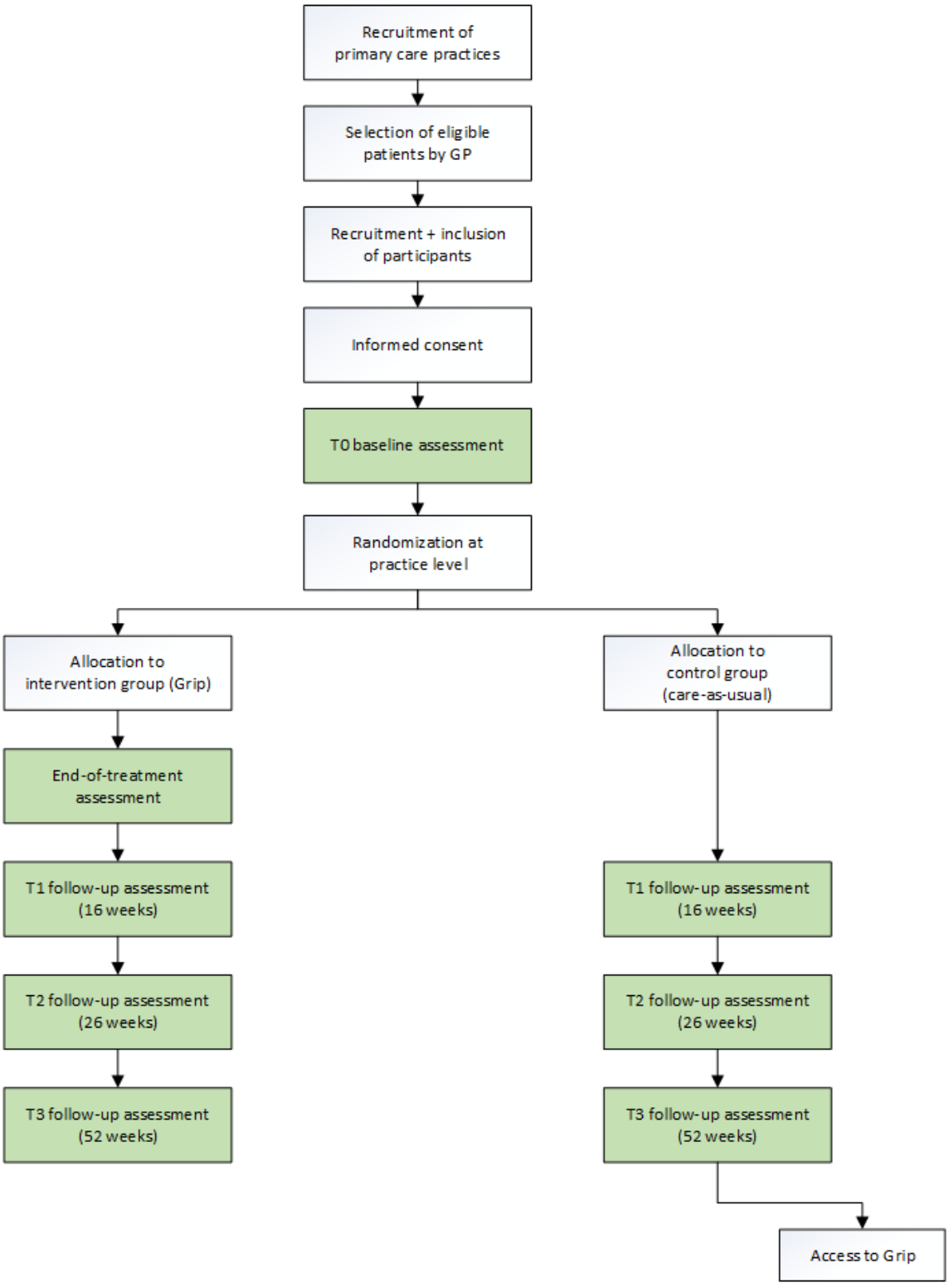
Inclusion criteria

- Age ≥18 years
- Presenting with mild to moderate medically unexplained symptoms (MUS). In line with the guidelines provided by the Dutch College of General Practitioners, MUS are defined as "physical symptoms that have persisted for more than several weeks and for which adequate medical examination has not revealed any condition that sufficiently explains the symptoms" [12]. MUS are considered mild to moderate in case of (1) mild to moderate functional limitations because of the symptoms, (2) symptoms in 1, 2 (mild), or 3 (moderate) symptom clusters (gastrointestinal symptoms, cardiopulmonary symptoms, musculoskeletal symptoms, and nonspecific symptoms), and (3) symptom duration longer than expected by the general practitioner
- Main symptom concerns pain, gastrointestinal complaints, or fatigue
- Adequate command of the Dutch language, no major cognitive or visual impairment

Exclusion criteria

- Referred to or currently treated by a mental health professional
- Start or adjusted dosage of psychotropic medication ≤3 months ago
- Likelihood of posttraumatic stress disorder (Trauma Screening Questionnaire ≥6 [13]), severe anxiety disorder (4-Dimensional Symptom Questionnaire or 4DSQ Anxiety ≥10 [14]), or severe depressive disorder (4DSQ Depression ≥6 [14])
- Pregnancy
- Engaged in a legal procedure concerning disability-related financial benefits
- Not in possession of an email account and a personal computer, laptop, or tablet with internet connection

Figure 1. Flowchart of the study procedure. GP: general practitioner.



Randomization Procedure

Randomization will be performed at general practice level. After all participants from a practice have given informed consent and filled out baseline questionnaires, practices will be randomly assigned to the intervention (Grip self-help) or control (CAU) group, using Web-based randomization tool ALEA (ALEA Clinical | FormsVision). Randomization after patient inclusion prevents the possibility of recruitment bias (selection bias). Randomizing general practices rather than patients will avoid PCPs within a practice offering both Grip self-help and CAU, as this could cause contamination effects. Randomization will take place in blocks, randomly varying in size between 4 and 8, and a 1:1 allocation ratio.

Control Group

Participants assigned to the control group will receive CAU during the study period. This could include care by the GP,

GP-MHW, physiotherapist, and a psychologist. After the last follow-up measurement at 52 weeks, participants assigned to the control group will be offered access to the study intervention.

Intervention Group

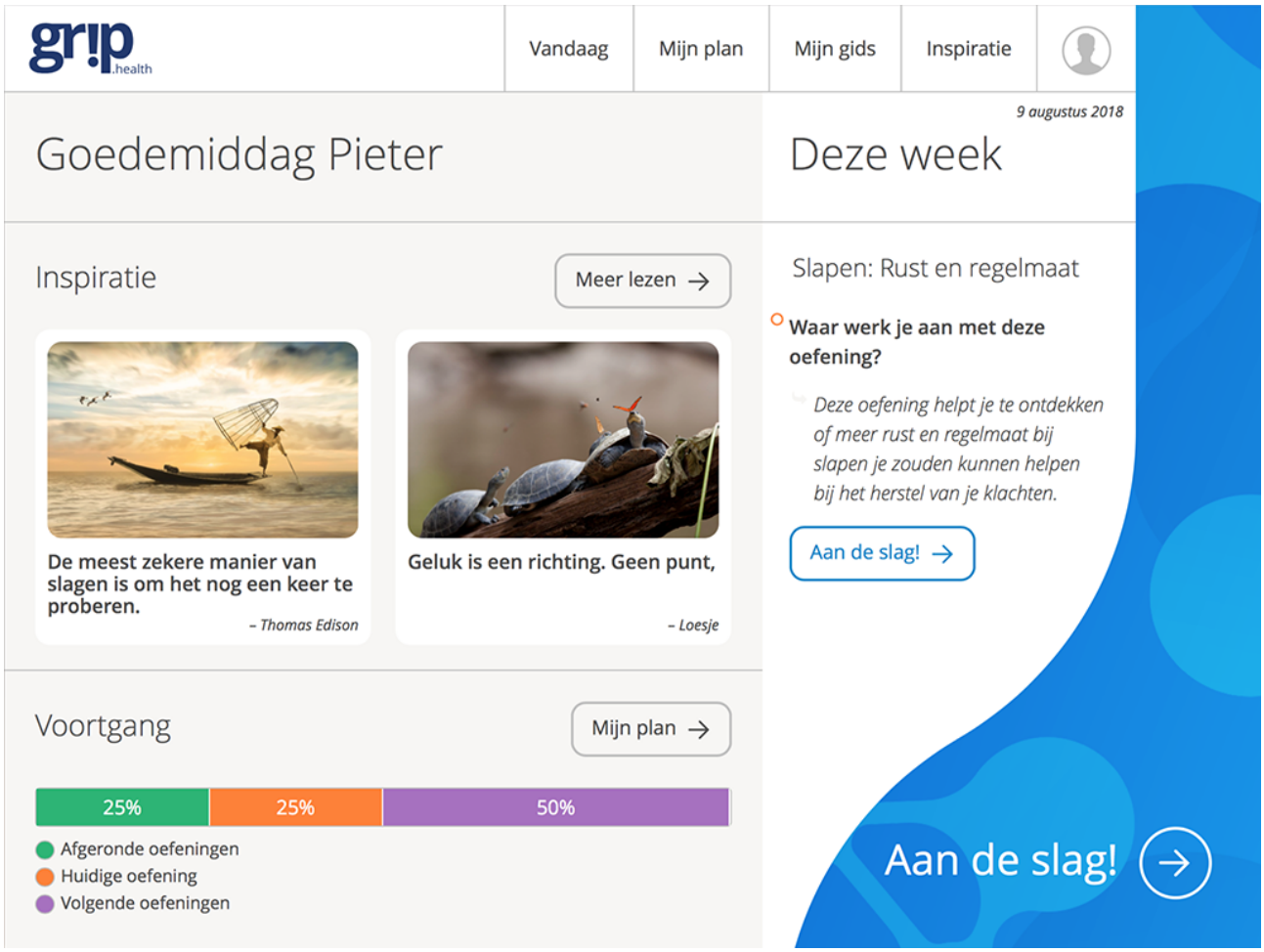
In addition to CAU, participants in the intervention group will be offered a Web-based self-help intervention called *Grip self-help*. Figure 2 shows a screenshot of the patient interface of the intervention.

The intervention comprises 2 steps. First, participants fill out a set of Web-based questionnaires concerning potential perpetuating factors: unhelpful cognitions, emotions, behaviors, and social factors associated with the physical symptoms. With this information, a personal problem profile is generated, identifying perpetuating factors that are relevant to the individual. Second, participants gain access to Web-based self-help exercises, selected using personalization algorithms based on their problem profile. Exercises are selected from a database, containing 59 unique exercises. Exercises include education, adjusting life style, identifying and challenging unhelpful cognitions, relaxation and mindfulness exercises, learning to accept the presence of physical symptoms and negative emotions, identifying values and setting goals accordingly, gradual exposure to feared activities, and managing the impact of symptoms on work and relationships. The exercises were not written from the perspective of a single therapeutic theoretical framework. Rather, they contain elements of cognitive behavioral therapy, acceptance and commitment therapy, and problem-solving treatment. The exercises vary with regard to duration (1 or 2 weeks) and intensity (varying from a single assignment to daily practice). Patients will work on 1 exercise at a time. The intervention will ultimately result in a personalized self-help guide, composed of texts that are extracted from the exercises patients found useful during the intervention.

The intervention is guided by the GP-MHW. A Web-based manual and technical support via email will be available to GPs and GP-MHWs allocated to the intervention group. These GPs and GP-MHWs will also be offered the option to take a free Web-based course on MUS and working with Grip.

GP-MHWs will be instructed to invite patients for at least two visits (start and finish). The frequency of further visits is left up to the GP-MHW. Although the exact length of the intervention will vary per person, we estimate that participating in the Grip self-help intervention on average takes 16 weeks. In 16 weeks, the participant will complete approximately 6 to 8 exercises.

Figure 2. Screenshot of the homepage of the patient interface of Grip self-help.



Outcomes and Assessments

Outcome measures at the patient level will be assessed at baseline, end of treatment, and follow-up after 16, 26, and 52 weeks. Physical HRQoL at 16 weeks, measured with the physical component score of the RAND-36, will be the primary outcome measure. Physical HRQoL at 26 and 52 weeks will be secondary outcome measures, as well as mental HRQoL, symptom severity (physical and psychological symptoms), and costs (health care utilization and productivity loss) after 16, 26, and 52 weeks. In addition, patient satisfaction with the study intervention will be assessed at 16 weeks and at the end of treatment. As the duration of the intervention will vary among participants, completion of the last self-help exercise is considered *end of treatment*. An overview of the assessment schedule can be found in Tables 1 and 2.

Table 1. Patient questionnaires and assessment schedule.

Questionnaire	Variable	T[a]0	End of treatment[b]	T1 (16 weeks)	T2 (26 weeks)	T3 (52 weeks)
Demographics	Age, sex, education, marital status	X	—[c]	—	—	—
RAND-36[d]	Physical and mental health–related quality of life	X	X	X	X	X
4DSQ[e]	Symptom severity physical and psychological symptoms	X	—	X	X	X
*i*MCQ[f]	Health care utilization	X	—	X	X	X
*i*PCQ[g]	Productivity loss	X	—	X	X	X
SCQ-8[h]	Patient satisfaction	—	X	X	—	—
SES[i]	Self-efficacy	X	X	X	—	—

[a]T: time point.

[b]End of treatment: after the last self-help exercise has been completed, these questionnaires are only filled out by participants in the intervention group.

[c]Not applicable.

[d]RAND-36: 36-item general health survey.

[e]4DSQ: 4-Dimensional Symptom Questionnaire.

[f]*i*MCQ: Medical Consumption Questionnaire.

[g]*i*PCQ: Productivity Costs Questionnaire.

[h]SCQ-8: Social Communication Questionnaire–8.

[i]SES: Self-Efficacy scale.

Table 2. Health care professional questionnaires and assessment schedule.

Questionnaire	Variable	T[a]0	End of treatment[b]	T1 (16 weeks)	T2 (26 weeks)	T3 (52 weeks)
MUS[c] attitude questionnaire	Attitude toward MUS	X	—[d]	—	—	—
DIBQ[e]	Determinants of implementation behavior	X	—	—	—	—
Electronic health attitude questionnaire	Attitude toward electronic health	X	—	—	—	—
SCQ-3[f]	Health care provider satisfaction	—	X	—	—	—

[a]T: time point.

[b]End of treatment: after the last patient has completed the last self-help exercise; these questionnaires are only filled out by health care professionals in the intervention group.

[c]MUS: medically unexplained symptoms.

[d]Not applicable.

[e]DIBQ: Determinants of Implementation Behavior Questionnaire.

[f]SCQ-3: Social Communication Questionnaire–3.

All instruments are self-report questionnaires. Participants will receive automated emails containing a link to the questionnaires. If participants have not filled out the questionnaires, automated email reminders will be sent after 1 and 2 weeks. If participants have not filled out the questionnaires after these reminders, a research assistant will call to remind them.

If participants decide to withdraw from the study before they have completed the study protocol, the main reason for

withdrawal will be inquired. Also, participants will be asked to complete the Web-based questionnaires at follow-up after 16, 26, and 52 weeks.

Instruments

Health-Related Quality of Life

We will use the validated Dutch version of the 36-item General Health Survey (RAND-36) to assess HRQoL. The RAND-36, which is nearly identical to the SF-36, is a self-report questionnaire for measuring general health status [15,16]. In this study, the 8 subscales will be aggregated into 2 summary scores: the physical and mental component score. The physical component score comprises 4 subscales: general health, bodily pain, physical functioning, and role limitations because of physical problems. The mental component score also comprises 4 subscales: vitality, mental health, social functioning, and role limitations because of emotional problems. Scores range between 0 and 100, with a higher score representing a better HRQoL.

Symptom Severity

Severity of MUS will be assessed with the Somatization subscale of the 4-Dimensional Symptom Questionnaire (4DSQ). The 4DSQ is a validated 50-item Dutch self-report questionnaire, developed and widely used in general practice to assess somatization, distress, anxiety, and depression [14]. The somatization subscale considers the frequency of 16 common physical symptoms over the past week with a score range between 0 and 32.

The 4DSQ will also be used to assess distress (subscale with 16 items, score range 0-32) and symptoms of anxiety (subscale with 12 items, score range 0-24) and depression (subscale with 6 items, score range 0-12). Higher scores refer to more symptoms.

Costs

The Medical Consumption Questionnaire (*i*MCQ) will be used to measure health care utilization. The *i*MCQ is a 31-item Dutch self-report questionnaire aimed to assess the direct costs of health care [17]. These are the costs of treatment, care and rehabilitation related to illness or injury and include expenditures for physicians and other health care professionals, care in hospitals and other institutions, and medication. We added extra items to the *i*MCQ to measure costs associated with contacts with a GP-MHW.

The Productivity Costs Questionnaire (*i*PCQ) will be used to assess productivity loss. The *i*PCQ is a 12-item Dutch self-report questionnaire aimed to measure indirect costs related to illness or injury [18]. These are the costs of productivity loss as a result of absence from work or inefficiency during paid or unpaid work.

Patient Acceptability

A Dutch translation of the Client Satisfaction Questionnaire-8 (CSQ-8) will be used to assess patient satisfaction with the study intervention [19]. The internal consistency of this scale in the Dutch population is very high. The 8-item self-report questionnaire has a score range from 8 to 32.

Other Variables

Demographic information (eg, age, sex, educational level, and marital status), internet experience, and type and severity of main presenting symptom will be assessed at baseline. As a mediator, self-efficacy will be assessed by the Self-Efficacy Scale [20].

In addition, the GP and GP-MHW will be asked to fill out a number of questionnaires. The PCP's attitude toward MUS will be assessed using a 24-item questionnaire. Potential determinants for health care professional implementation behavior will be examined using a selection of 13 items from the Determinants of Implementation Behavior Questionnaire [21]. The PCP's attitudes with regard to risks and benefits of electronic health (eHealth) and their own computer skills will be assessed with the Dutch 18-item eHealth Attitude Questionnaire [22]. To assess PCP acceptability of Grip self-help, PCPs in the intervention group will complete the core item set of the CSQ-8, adjusted for use by health care professionals (CSQ-3).

Sample Size

Our power analysis is based on the effect estimates, calculated in our previous meta-analysis on the effectiveness of self-help interventions for MUS [11]. For HRQoL, we observed an effect size (Hedges g) of 0.66. As there was some evidence of publication bias toward larger effect sizes and because this meta-analysis also included studies with a waiting list control group, we based our calculations on an effect size of 0.5 (moderate effect). Without correcting for clustering by practice, the sample size based on an unpaired *t* test, given an effect size of 0.5, adopting power (1−beta) of .8, and alpha .05 2-sided, is 128. Accounting for 20% dropout, the number of patients that needs to be included is 1.25×128=160. On the basis of previous Dutch studies on MUS in general practice, we expect that a GP can include 4 patients during the inclusion period. To adjust the sample size for clustering by GP we calculated the design factor as: 1+(cluster size−1)×intraclass correlation coefficient (ICC). ICCs of 0.01 are recommended for the primary care setting [23], and the design factor then is 1+(4−1)×0.01=1.03. Consequently, a total of 1.03×160=165 patients need to be included, with an estimated number of 41 GPs.

Statistical Analyses

Primary analysis will be performed on an intention-to-treat basis, meaning that all subjects that were allocated to either the intervention or the control group are included in the analysis and analyzed in the groups to which they were randomized. Secondary analyses will be performed on a per-protocol basis. The Grip self-help intervention is considered per-protocol if the last exercise has been completed. If, despite randomization, important baseline differences exist in prognostically important variables, they will be adjusted for by including them as covariates.

Differences in the effectiveness of Grip self-help compared with CAU will be analyzed using linear mixed-models (LMM), with HRQoL (RAND-36) and symptom severity (4DSQ) as outcomes. LMM allow correcting for dependence of (repeated) observations within patients as well as possible variations

between practices. LMM have shown to be superior for the analysis of longitudinally correlated data and can optimally deal with missing values (no imputation needed) and cluster effects [24].

For the remaining analyses, missing values will be imputed using multiple imputation (MI). Both LMM with incomplete data and MI require the assumption of data being missing at random. Although this assumption is not testable, we will study the missing data mechanism by studying predictors of *missingness* of data using multivariable logistic regression analyses. The final imputation model will comprise all variables used in the analyses and all variables that predict *missingness* of a certain variable or its value.

The cost-effectiveness of Grip self-help compared with CAU will be investigated from a societal perspective, which includes costs in- and outside the health care sector (*i*MCQ and *i*PCQ). Results will be expressed in terms of incremental costs per quality-adjusted life year gained.

Acceptability of the Grip self-help intervention for patients and PCPs will be assessed using CSQ-8 and CSQ-3 scores.

To investigate which patient characteristics predict effectiveness of Grip self-help, Least Absolute Shrinkage and Selection Operator linear regression will be performed in the intervention group. Interaction terms of demographic variables and problem profile scores x treatment group will be entered as predictors, the physical component score of the RAND-36 at the end of treatment will be the outcome. For these analyses, the MI procedure will be performed separately in the treatment groups to allow for different associations between predictor and outcome in the Grip self-help and control condition.

To investigate which characteristics of PCPs predict effectiveness of Grip self-help, analyses of subgroups of these characteristics (eg, attitude toward MUS, eHealth attitude, and determinants for implementation behavior) will be performed, followed by statistical significance testing of the pertaining subgroup indicator xGrip self-help interaction term. As our sample calculation did not reckon with subgroup analyses, we consider these analyses exploratory in nature.

To investigate whether increased self-efficacy mediates treatment outcomes, we will use the regression-based method proposed by Preacher and Hayes [25].

Results

Inclusion of PCPs started in December 2018, and enrolment is ongoing. The first results are expected to be submitted for publication in December 2021. Results will be reported according to the eHealth extension of the Consolidated Standards of Reporting Trials statement [26].

Discussion

Challenges

This paper presents the design of an RCT assessing the effectiveness and cost-effectiveness of Grip self-help: a personalized, Web-based, guided self-help intervention for patients with mild to moderate MUS in primary care.

Conducting this trial will involve several operational challenges. The first challenge is the recruitment of an adequate number of PCPs and participants. As an incentive, GPs are given €50 per included patient. However, as patients are selected by their GP based on past visits, there is a chance that patients are not experiencing current symptoms or difficulties and, therefore, are not motivated to participate in the study. Second, there is a chance of dropout in the control group, as these patients will not gain immediate access to the study intervention. This might lead to a lack of motivation to take part in follow-up assessments. To account for this challenge, patients in the control group will be offered access to the Grip self-help intervention after completion of the study. The last challenge is the potential nonusage of the Grip intervention. Previous studies have shown that nonadherence is a common problem in Web-based interventions [27]. To prevent nonusage, we have taken several measures. Patients will receive reminders when they have not logged into the Web-based platform. Also, the platform includes daily inspirational quotes and blogs to encourage daily use. In addition, log data enable us to track the amount of time patients spend using the intervention. Finally, guidance by the GP-MHW is offered throughout the intervention to motivate patients, answer questions, and overcome difficulties.

Strengths and Limitations

Apart from these challenges, there are several strengths and limitations to the study. First, the Grip self-help intervention has a number of important strengths. As the intervention is provided in general practice, the intervention is easily accessible to a large group of patients. We hereby hope to also reach patients, who might not be willing to visit a mental health care facility to receive treatment. Also, the intervention is easy to implement in general practice because it is coherent with the current ways of working of PCPs. Strengths with regard to the study design are the follow-up period of 1 year, which allows for studying long-term effectiveness. Also, randomizing practices instead of patients will prevent contamination effects.

Of course, there are also a number of limitations to this study. First, self-selection of PCPs participating in the study may lead to selection bias, with an overrepresentation of PCPs having a special interest in either MUS or eHealth interventions. Second, the selection of patients by GPs also potentially causes selection bias. However, randomization takes place after the selection of patients, which limits this potential form of bias. Third, because of the nature of the intervention, patients, PCPs, and researchers will not be blinded to the study condition. This may lead to bias. Finally, outcome measures will be assessed using Web-based questionnaires. Although nearly all of the selected instruments were validated, traditional paper-and-pencil questionnaires were used in validation studies. This is of concern because psychometric properties might differ between different types of administration. However, several reviews have shown that Web-based testing usually produces very similar results compared with traditional testing [28,29].

Conclusions

To our knowledge, this is the first study to combine the concepts of eHealth, self-help, and personalized medicine in the treatment of MUS. By improving the quality of life and reducing symptoms of patients with MUS, the Grip self-help intervention has the potential to reduce costs and conserve scarce health care resources.

Acknowledgments

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Authors' Contributions

JR conceived of the study and obtained funding. JR, DH, and AvG designed the study intervention. JR, DH, AvG, AvA, and HB contributed to the study design. AvG drafted the paper. JR, DH, AvA, and HB revised it. All authors read and approved the final paper.

Conflicts of Interest

JR, DH, and AvG are the developers of the Grip self-help intervention; however, they have no commercial/financial interest. HB and AvA have no conflicts of interest.

Multimedia Appendix 1
Peer review report from funding body 1.
[PDF File (Adobe PDF File), 59 KB - resprot_v8i10e13738_app1.pdf]

Multimedia Appendix 2
Peer review report from funding body 2.
[PDF File (Adobe PDF File), 64 KB - resprot_v8i10e13738_app2.pdf]

Multimedia Appendix 3
Peer review report from funding body 3.
[PDF File (Adobe PDF File), 58 KB - resprot_v8i10e13738_app3.pdf]

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Abbreviations

4DSQ: 4-Dimensional Symptom Questionnaire
CAU: care-as-usual
CSQ-8: Client Satisfaction Questionnaire-8
eHealth: electronic health
GP: general practitioner
GP-MHW: general practice mental health worker
HRQoL: health-related quality of life
ICC: intraclass correlation coefficient
iMCQ: Medical Consumption Questionnaire
iPCQ: Productivity Costs Questionnaire
LMM: linear mixed-models
MI: multiple imputation
MUS: medically unexplained symptoms
PCP: primary care professional
RAND-36: 36-item general health survey
RCT: randomized controlled trial

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Protocol

An Online Minimally Guided Intervention to Support Family and Other Unpaid Carers of People With Dementia: Protocol for a Randomized Controlled Trial

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Abstract

Background: About three-quarters of people with dementia live in their own homes, with help from family members and/or other unpaid carers, such as friends or neighbors. Often, unpaid carers themselves experience negative consequences, such as stress, burden, and symptoms of depression or anxiety. Research has shown that these consequences can be alleviated by psychosocial and psychological interventions. Moreover, there are indications that those interventions can be effective when offered online.

Objective: This paper describes the protocol of a randomized controlled trial (RCT) that will take place in the Netherlands to evaluate the effectiveness of iSupport, a minimally guided, internet-based intervention to improve carers' mental health and coping resources.

Methods: A superiority two-arm RCT comparing the effects of the online support program with a waiting list control condition will be carried out in the Netherlands. The iSupport intervention was developed by the World Health Organization and is based on cognitive behavioral therapy principles. It has five main themes divided into 23 lessons. Carers can pick and choose which lessons they want to complete. We aim to recruit 200 unpaid carers. The experimental group (n=100) will be provided with access to the intervention for 3 months following randomization; those in the waiting list control group (n=100) will be granted access to the intervention after 3 months. Assessments will be conducted at baseline (T0), 3 months after baseline (post intervention, T1), and 6 months after baseline (follow-up, T2). The primary outcome is perceived stress, measured by the Perceived Stress Scale. Secondary outcomes are symptoms of depression and anxiety, caregiver burden, sense of competence, self-efficacy, mastery, and carers' attitudes toward dementia and their person-centered approach (ie, to what extent carers tailor the provided care to the interest, needs, and history of the person with dementia).

Results: Recruitment for the trial started in January 2019. As of July 2019, we have enrolled 120 participants. Data collection is expected to be completed by March 2020. Once all the data have been collected, we will conduct the data analyses between April and May 2020. We aim to publish our results in a manuscript by June 2020.

Conclusions: Online interventions have shown promising results in improving the mental health of carers of people with dementia. Additionally, online interventions may overcome accessibility barriers. If successful, this intervention will have important potential for implementation as a public health intervention, since costs and support by trained staff are minimal.

Trial Registration: Netherlands Trial Register (NTL) NL6417; https://www.trialregister.nl/trial/6417
International Registered Report Identifier (IRRID): DERR1-10.2196/14106

(JMIR Res Protoc 2019;8(10):e14106) doi:10.2196/14106

KEYWORDS

informal carers; dementia; ICT intervention; online; perceived stress

Introduction

It is expected that the number of people with dementia will grow exponentially in the coming years; most of them will be cared for by family and other unpaid carers [1,2]. In Europe, families and other unpaid carers provide about 75% of the care or supervision for people with dementia living at home, including help with activities of daily living, finances, and arranging care such as scheduling appointments with professionals [3,4]. The provision of unpaid care often affects carers' lives negatively. They are prone to feelings such as stress, depression, anxiety, and being overburdened when providing care for a prolonged period of time [5]. This is especially notorious in dementia where the person becomes increasingly dependent on care during the course of the disease [6].

Consequently, the World Health Organization (WHO) identified family members' and other unpaid carers' need of support as a key priority [4,7]. The Dutch government also framed the improvement of the quality of life of carers of people with dementia as a health priority. One of the objectives of the Dutch dementia strategy is to develop and implement new care models with effective tools and interventions for both people with dementia as well as their unpaid carers [8].

In recent years, several types of interventions have been developed to ameliorate the health and well-being of carers of people with dementia. Examples are psychoeducational programs, cognitive behavioral therapy (CBT), respite care, and occupational therapy [9]. Psychological treatments aimed at improving carers' ability to cope with problematic behavior, to cope with stressful situations, to enhance communication with the person with dementia, and to ask for support from others have been demonstrated to be effective in improving carers' mental health and well-being [10-12]. Despite the progress of psychological face-to-face interventions specifically designed for carers of people with dementia, most carers still do not use or are unable to access this professional support because they are unaware of its existence, they have time constraints, or they do not want psychological help (ie, negative attitude possibly reinforced by cultural influences) [7]. Online interventions may be an effective solution to overcome these accessibility barriers. Previous research has found promising results of online interventions even when compared to face-to-face interventions [13-18]. Unguided interventions are generally seen as less effective than those that are guided by a therapist or coach, whether online or by telephone [16]. However, unguided or minimally guided interventions have the advantage that they can be easily scaled up because no extensive input of a therapist is needed. Additionally, online interventions in any format are advantageous for people because they do not have to schedule specific appointments and they do not need to travel to any particular setting. Furthermore, online interventions might help reduce the stigma that still remains in society regarding dementia and receiving psychological support as a carer. Therefore, with the help of an international expert panel, the WHO has developed iSupport, an online knowledge and skills training program, which aims to improve carers' mental health and coping resources. iSupport is based on psychoeducation and CBT techniques, such as activity scheduling, relaxation, and cognitive reframing. A first adaptation of iSupport has been carried out for India. A pilot study was carried out with the adapted English version in India from 2017 to 2018 [19]. For our study, we translated iSupport into Dutch and adapted the text in line with the WHO's adaptation and implementation guide for the Netherlands.

Currently, families and other unpaid carers in the Netherlands can find information, training, and support through a wide variety of online internet resources. These resources include the following: informative websites (eg, dementie.nl, owned by the Alzheimer's Association in the Netherlands); an online social support intervention [20]; free and paid apps to organize family care, organize other unpaid care, and increase peer support to improve communication between carers [21]; a self-guided, e-learning course with different levels of knowledge tailored to the needs of unpaid and professional dementia carers [18]; and a guided internet intervention to reduce psychological distress of caregivers of people with dementia with online coaching by a mental health professional [22,23].

iSupport is an addition to this broad spectrum of internet interventions. As an online training and support program with minimal guidance, iSupport focuses on mental health outcomes of family and other unpaid carers. The iSupport program is flexible (ie, carers can select the topics they prefer) and personalized (ie, provides automatically personalized feedback). This paper describes the design of a randomized controlled trial (RCT) to examine the effectiveness and usability of iSupport for family and other unpaid carers of people with dementia; we examined the tool's ability to reduce carers' distress and improve mental health (eg, depression and anxiety symptoms and caregiver burden) and to increase coping resources (eg, mastery, self-competence, and self-efficacy) compared to a waiting list control group.

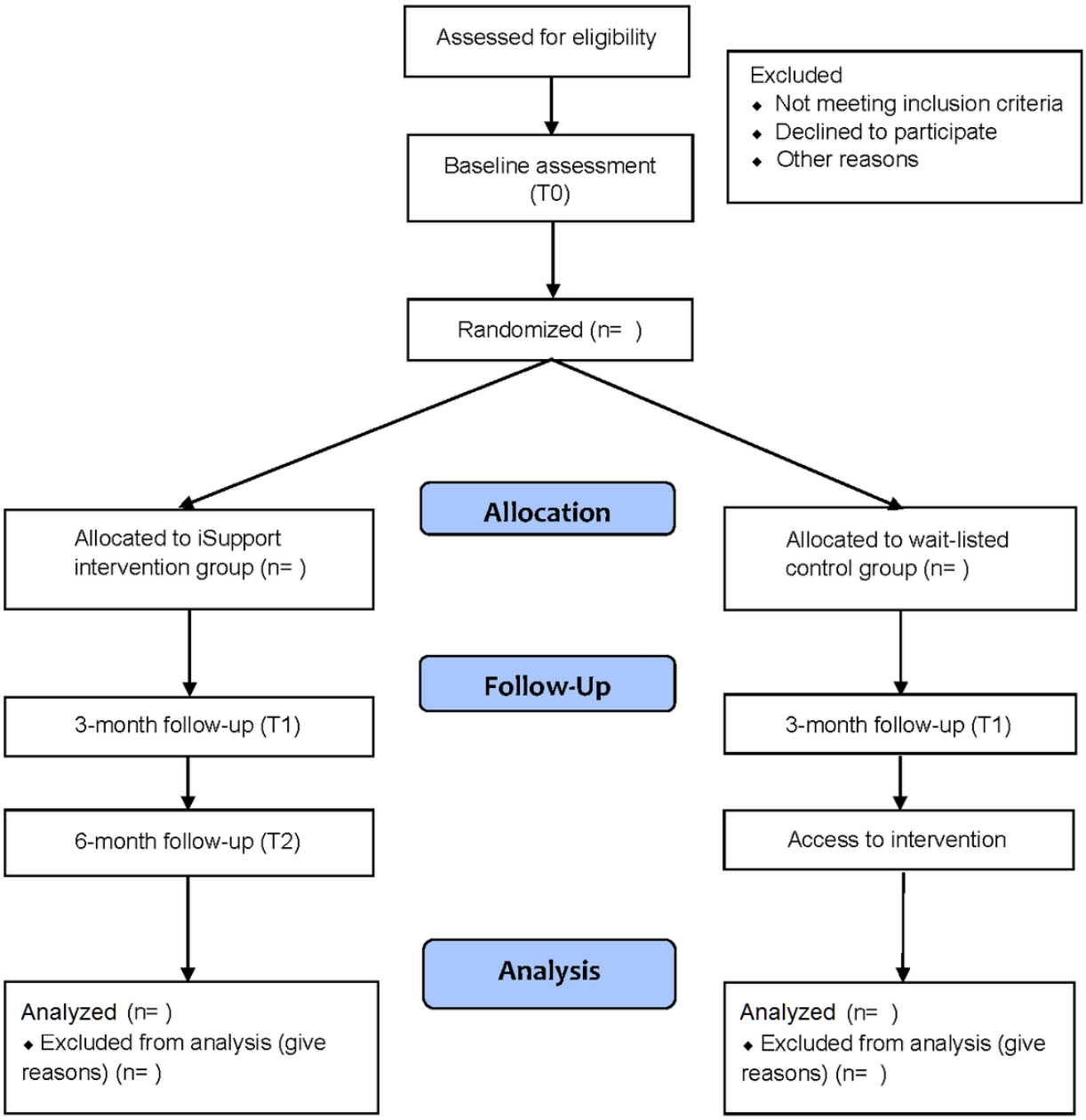
Methods

Study Design

The study has been designed as a two-arm superiority RCT. Carers will be randomized to (1) the intervention group that will use iSupport, an online training and support program, or (2) a waiting list control group. The iSupport intervention group will be provided with access to the intervention for 3 months

immediately following the randomization; those assigned to the control group will receive access to iSupport 3 months after randomization (see Figure 1). The study will be carried out according to the Consolidation Standards of Reporting Trials (CONSORT) guidelines [24].

Figure 1. Consolidation Standards of Reporting Trials (CONSORT) diagram for this study.



Inclusion and Exclusion Criteria

The potential participants will be relatives or other unpaid carers of people with dementia. The participants must be at least 18 years old. We will focus on unpaid carers who are providing care to a family member, friend, or neighbor for at least 6 months, regardless of the number of hours per day they spend on care provision. To be included in the study, their well-being will need to have been affected at least to some extent. We will measure well-being via levels of stress, existence of depressive or anxiety symptoms, or experience of caregiver burden. This means that the carers will need to have a score greater than 13 on the Perceived Stress Scale (PSS) [25], a score of 4 or greater on the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) [26], or a score of 4 or greater on the Centre for Epidemiological Studies Depression scale (CES-D) [27]. Caregiver burden will be assessed using a one-item scale with a score ranging from 1 (no burden) to 10 (extreme burden); people will be eligible for the study if they scored 4 or greater.

Furthermore, there needs to be an indication that the person that is being cared for is indeed living with dementia. Therefore, carers will have to fill out the Ascertain Dementia 8-item informant questionnaire (AD8) [28]. The AD8 assesses the functional decline of the person with dementia attributed to cognitive impairment over the past years as reported by the

carer. In order to be included, the score needs to be 2 or higher. This cutoff has been shown to have a good discriminative validity between people with and without dementia. We will also ask whether or not the person has been officially diagnosed with dementia, but this will not serve as an inclusion criterion.

We will exclude people who are unable to comprehend written Dutch or have no access to the internet. If both groups differ regarding the professional support they have received, we can control for it in the analyses, but receiving professional support will be not be used as an exclusion criterion.

Recruitment of Participants and Study Procedure

People will be recruited through different sources. First, Alzheimer Nederland (AN), the Dutch Alzheimer's national association, will place announcements about the study on their website, social media pages, and newsletter, among other places. Second, study banners will be placed on other relevant websites. Third, the research team will leave brochures and posters while visiting Alzheimer's cafés and memory clinics. All of our study announcements will refer to our study website [29], which contains information about the study purpose and procedures. Those who are interested in participating will be able to register through this study website. We will then contact them via email where we will include a brochure with the information and a link to the online battery of baseline questionnaires, which includes the screening questions and the online written informed consent form. At this stage, we will fully inform potential participants about the aim and procedures of the study and will again ask for online informed consent. Based on the answers to the screening questions from the battery of baseline questionnaires, we will check the inclusion and exclusion criteria. Those who do not fulfil our inclusion criteria or do not provide informed consent will not be able to continue to fill out the remainder questionnaires of the baseline battery. They will receive an automated message explaining why they cannot participate in the study. We will stress that they can consult their general practitioner and AN at any time. Those who fill out the full battery of baseline questionnaires and fulfil the inclusion criteria will be included in the study and will be randomized. The outcome of the randomization will be communicated to participants via email. Participants randomized to the iSupport group will receive the intervention log-in details and they will have access to the intervention for 3 months. After the third month, participants will no longer have access to the intervention. Those who are randomized to the waiting list control group will be informed that they will receive log-in details for iSupport after they have completed the 3-month assessment. They will be free to seek any help they want in the meantime. The postintervention measurement and follow-up measurement will be sent via email 3 months and 6 months after randomization, respectively.

Ethical Approval

The trial will be conducted according to Dutch and European legal requirements and standards as well as the Declaration of Helsinki (World Medical Association, 2013). The study protocol was reviewed by the Ethical Committee of the Faculty of Behaviour and Movement Sciences of the Vrije Universiteit Amsterdam (approval number: VCWE-2017-126); according to the review by the Medical Research Ethical Committee of the Vrije Universiteit medical center, this study does not fall within the scope of the Medical Research with Human Beings Act (review number: 2017.331).

Randomization and Blinding

A randomization schedule with a 1:1 allocation ratio will be made with a computerized random number generator using variable block sizes of two and four by an independent researcher. We will stratify for gender and for the type of relationship between the carer and the person with dementia (ie, partner or other). After every inclusion, the same independent researcher will reveal the next randomization outcome so that allocation is concealed. Participants will be informed about the randomization outcome by email.

Intervention: iSupport

iSupport is an online support program used to enhance self-care skills and support carers of people with dementia. The intervention has been developed by the WHO in collaboration with international experts in the field and Alzheimer Disease International. Final content decisions of the generic version were based on the outcomes of focus groups with professionals and unpaid carers, a pilot study (N=10) in India, and discussion within the project group. iSupport is based on the principles of CBT and includes techniques such as problem solving, relaxation, and cognitive reframing. During the development of the intervention, ethical principles and the needs of the carers were considered.

iSupport consists of 23 lessons distributed over five modules: (1) What is dementia? (one lesson), (2) Being a caregiver (four lessons), (3) Caring for me (three lessons), (4) Providing everyday care (five lessons), and (5) Dealing with challenging behavior (10 lessons). In Table 1, an overview of the topics covered through all modules and lessons is presented.

Carers may pick and choose which lessons they would like to do, depending on their needs and how relevant the topic of the lesson is to them. Every lesson follows the same format, consisting of information about the main topic of the lesson; small exercises, after which participants receive instant personalized automated feedback; and a summary of the lesson plus a relaxation exercise. In order to personalize the feedback and the content of the intervention, participants are asked to provide their own name, the name of the person with dementia, their relationship, and some other basic demographics (ie, gender and age). The program can be followed via the internet on a personal computer or tablet.

Table 1. Modules and lessons from iSupport.

Modules	Lessons
1. What is dementia?	1.1. Introduction to dementia
2. Being a caregiver	2.1. The journey together
	2.2. Communication
	2.3. Shared decision making
	2.4. Involving others
3. Caring for me	3.1. Reducing stress in everyday life
	3.2. Pleasant activities
	3.3. Thinking differently
4. Providing everyday care	4.1. Eating and drinking: more pleasant mealtimes
	4.2. Eating and drinking: preventing health problems
	4.3. Toileting and continence care
	4.4. Personal care
	4.5. Enjoyable day
5. Dealing with challenging behavior	5.1. Introduction to challenging behaviors
	5.2. Memory loss
	5.3. Aggression
	5.4. Depression and anxiety
	5.5. Difficulty sleeping
	5.6. Delusions and hallucinations
	5.7. Repetitive behaviors
	5.8. Walking and getting lost
	5.9. Poor or decreased judgement
	5.10. Putting it all together

Participants will be advised to use the iSupport program regularly to benefit as much as possible from their participation. It is anticipated that carers will be able to complete the whole program in 3 months. Participants will be able to indicate that they want some personal contact by sending their email address to our e-coaches. They will then be contacted by an e-coach three times via email: right after the first email, 1 month later, and 2 months later. Additionally, carers may contact the e-coach, if necessary, at any point of the intervention, although we aim not to have more than 10 interactions between e-coaches and participants. The purpose of the e-coach is to encourage participants to continue with the iSupport program, to explain anything that is not clear to the carer in the iSupport program, and to help to find additional support if needed. The emails that are sent by the users will be anonymized and used to improve the iSupport program. The coaches will be volunteers currently working for the telephone helpline of AN. They will complete a 4-hour training session by members of the research team in order to fully comprehend the intervention and the study.

The generic iSupport intervention is in English. However, during the developmental stages, attention has been paid to the possibility of adapting the intervention to different languages and cultural and economic situations. We adapted the generic version to the Dutch context. This means that the intervention has been translated by an official translator, who is knowledgeable in the field of dementia care, following the adaptation and implementation guide provided by the WHO. All text not pertinent to Dutch culture has been adapted (ie, names, activities, timetables, email addresses, etc). Afterward, the text was reviewed by staff of AN and an independent reviewer to ascertain that the adaptation was accurate and a dementia-friendly vocabulary was used.

Intervention: Waiting List Control Group

Participants assigned to the waiting list condition will receive access to the iSupport intervention 3 months after the baseline session. We will stress that carers allocated to this group will be allowed to access any help they may need from online resources, to participate in support groups, or to access any type of professional help.

Assessments

All assessments will be administered online and consist of a variety of self-reported measures. During the first measurement, we will assess the inclusion and exclusion criteria. Only those people that are eligible will complete the remainder of the baseline questionnaires. Table 2 provides an overview of the questionnaires and the number of items for each assessment.

Primary Outcome

Our primary outcome is perceived stress. Perceived stress will be assessed with the PSS [25]. The PSS is a 14-item scale designed to measure global levels of stress and to assess to what extent participants perceive their lives as unpredictable, uncontrollable, and overloaded. Each item is scored on a Likert-type scale from 0 (never) to 4 (very often). The total score ranges from 0 (no stress) to 88 (very stressed).

Table 2. Overview of measures.

Collected data and instrument	Outcome measures	Items, n	T0[a]	T1[b]	T2[c]
Demographic data of carers and persons with dementia					
Sociodemographic questions	Age, gender, etc[d]	15	x[e]	N/A[f]	N/A
Inclusion criteria					
Burden scale	Caregiver burden	1	x	N/A	N/A
AD8[g]	Functional decline	8	x	N/A	N/A
Primary outcome					
PSS[h]	Perceived stress	14	x	x	x
Secondary outcomes					
Mental health					
CES-D[i]	Depression	20	x	x	x
HADS-A[j]	Anxiety	7	x	x	x
ZBI[k]	Caregiver burden	12	x	x	x
Mastery and sense of competence					
PMS[l]	Mastery	7	x	x	x
RIS[m] Elder Care Self-Efficacy Scale	Self-efficacy	10	x	x	x
SSCQ[n]	Sense of competence	2	x	x	x
Attitude toward dementia and the care recipient					
ADQ[o]	Approaches to dementia	11	x	x	x
Treatment adherence, usage, and satisfaction					
SUS[p]	Usability	10	N/A	x	N/A
Postlesson questions	Satisfaction	2 per lesson	N/A	x	N/A
Analysis of platform data	Intervention usage	N/A	N/A	x	N/A

[a]T0: baseline assessment.

[b]T1: 3-month follow-up assessment.

[c]T2: 6-month follow-up assessment.

[d]Demographic data of carers: age, gender, marital status, number of children, children living at home, relationship with the person with dementia, level of education, months of caregiving, and average days per week providing care. Demographic data of persons with dementia: age, gender, marital status, living situation, and diagnosis.

[e]The questionnaire is included at the questionnaire battery for the different time points (T0, T1, T2), in opposition to N/A.

[f]Not applicable.

[g]AD8: Ascertain Dementia 8-item informant questionnaire.

[h]PSS: Perceived Stress Scale.

[i]CES-D: Centre for Epidemiological Studies Depression scale.

[j]HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale.

[k]ZBI: Zarit Burden Interview.

[l]PMS: Pearlin Mastery Scale.

[m]RIS: relational self-efficacy, instrumental self-efficacy, and self-soothing efficacy.

[n]SSCQ: Short Sense of Competence Questionnaire.

[o]ADQ: Approaches to Dementia Questionnaire.

[p]SUS: System Usability Scale.

Secondary Outcomes

Our secondary outcomes are related to (1) mental health (ie, symptoms of depression, anxiety, and caregiver burden); (2) mastery and sense of competence; (3) attitude toward dementia and the care recipient (ie, person-centered approach); and (4) intervention usability, intervention use, and satisfaction with the content of the intervention.

Anxiety symptoms will be measured using the Dutch version of the HADS-A. The HADS-A [26] consists of seven items concerning anxiety complaints experienced in the past week. Subjects will score these feelings on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day); the total score will range from 0 (no anxiety) to 21 (many anxiety symptoms).

Depressive symptoms will be measured with the CES-D [27]. This Likert-type scale consists of 20 items for which subjects will rate the frequency of symptoms during the past week. Scores range from 0 (rarely present or present none of the time: less than one day) to 3 (present most or all of the time: 5-7 days). The total score will range from 0 (no depression) to 60 (very depressed).

Perceived caregiver burden will be measured with the 12-item Zarit Burden Interview (ZBI) [30,31]. The scale measures a number of different types of burden, including the emotional, social, and financial impact of caring for someone. Each of the 12 items will be scored on a 5-point Likert scale from 0 (never) to 4 (nearly always). The total score will range from 0 (no burden) to 48 (very high burden).

Mastery will be measured using the 7-item Likert-type Pearlin Mastery Scale (PMS) [32,33]. The item scores range from 1 to 5, hence, the total scale score will range from 7 to 35. A high score represents internal mastery and indicates that someone has the feeling of being in control of situations. A low score represents external mastery and indicates that someone has the feeling that things are outside of their control.

Next, we will measure the feelings of self-efficacy with the relational self-efficacy, instrumental self-efficacy, and self-soothing efficacy (RIS) Elder Care Self-Efficacy Scale [34]. This scale measures the extent to which someone believes they are able to successfully master a specific task [35]. The scale consists of three subscales: (1) relational self-efficacy (three items): beliefs about one's ability to maintain a cooperative and harmonious relationship with the recipient of care, (3) instrumental self-efficacy (four items): beliefs about one's ability to accomplish tasks associated with the provision of personal care, and (3) self-soothing efficacy (three items): beliefs about one's ability to maintain their own well-being in the midst of emotionally taxing and usually unrelenting demands. Each of the 10 items is rated on a 5-point Likert scale ranging from 1 (I'm certain I can't do this) to 5 (I'm certain that I can do this). The subscale scores are derived by summing the item scores. Higher scores indicate increased self-efficacy.

We will measure sense of competence using the Short Sense of Competence Questionnaire (SSCQ) [36], which consists of seven items, five of which are already included in the ZBI. This means that we will ask participants to address the two remaining items. Three domains are distinguished in the SSCQ: (1) satisfaction with the person with dementia as a recipient of care, (2) satisfaction with one's own performance as a carer, and (3) consequences of involvement in care for the personal life of the carer. Each item is scored on a 5-point Likert scale, ranging from 1 (agree very strongly) to 5 (disagree very strongly). The total score will be derived by summing up the item scores.

The relationship between the carer and the person with dementia will be assessed with one of the subscales from the Approaches to Dementia Questionnaire (ADQ) [37]. This 11-item subscale measures *recognition of personhood*. This reflects the extent to which people have a person-centered understanding of dementia. It assesses to what extent the carer recognizes the care recipient as a unique and valuable individual. Each item will be answered on a 5-point Likert scale ranging from 1 (completely agree) to 5 (completely disagree). The total score will be a summation of the item scores and will range from 11 to 55. Higher scores will indicate more positive attitudes regarding personhood toward people with dementia.

We will use the 10-item System Usability Scale (SUS) [38] to evaluate the overall usability of the iSupport program. This questionnaire was specifically developed to evaluate information and communications technology products, websites, and applications. Each item is a statement and the respondent will need to indicate to what extent they agree with the statement on a 5-point Likert scale, ranging from 0 (strongly agree) to 4 (strongly disagree). An example of a statement is "I thought iSupport was easy to use." The total score will range from 0 to 40 and will be multiplied by 2.5 to convert the scores to 0-100.

We will gather data about participant satisfaction from the completed lessons: after every lesson, carers will be asked two questions about how satisfactory the lesson was for them. The use of iSupport will be assessed by downloading track-and-trace data. We will examine the number of log-ins, the total time spent on the intervention, and the number of completed lessons.

Finally, we will also gather information on sociodemographic variables. For carers, we will collect information on the following: age, gender, relationship to the person they are caring for, civil status, level of education, average hours of care per week, and living arrangements (ie, cohabiting or not with the person they are caring for). For the person with dementia, we will collect information on the following: age, gender, existence of an official diagnosis, type of dementia, and time since the diagnosis was given.

Sample Size

Perceived stress is our primary outcome measure and is used for the power calculation. Based on the results of a previous study about an online intervention for carers [39], we expect an effect size (Cohen *d*) of 0.40. Assuming an alpha of .05 and a statistical power (1-beta) of .80 in a two-tailed test, we will need 100 respondents in each of the conditions, resulting in a total of 200 participants. Calculation of the sample size was carried out with G*Power 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf) [40].

Statistical Analysis

We will first check whether or not the randomization was successful by comparing the two groups for all baseline variables with *t* tests for continuous data or chi-square tests for dichotomous data. We will also check for differences between study dropouts and those who remain in the study at 3 months. The primary analyses will be based on the intention-to-treat principle. Sensitivity analyses will be performed only with those participants that filled out the pre- and posttest questionnaires

(ie, completers). Missing data handling will depend on the amount and pattern of missing data, selecting the most appropriate technique. We will use the generalized estimating equation to examine the association between changes in stress scores (ie, PSS scores) and treatment arms (ie, iSupport vs waiting list). We will correct for baseline scores if they are not equally distributed. We will examine the influence of age, gender, and relationship (ie, spouses vs other relationship) on the outcomes. These analyses will be repeated for burden, anxiety and depression, sense of competence, self-efficacy, and mastery. Next, we will express the between-group, posttest, effect sizes for the different outcomes using Cohen *d*. Cohen *d* is the difference between the two posttest means divided by the pooled standard deviation. An effect size of 0.8 is considered to be large, an effect size of 0.5 is considered to be moderate, and an effect size of 0.2 is considered to be small.

Results

Recruitment for the trial started in January 2019. As of July 2019, we have enrolled 120 participants. Data collection is expected to be completed by March 2020. Once all the data have been collected, we will conduct the data analyses between April and May 2020. We aim to publish our results in a manuscript by June 2020.

Discussion

In this paper, we outlined the design of an RCT to examine the effectiveness of iSupport for families and other unpaid carers of people with dementia in improving their mental health and coping strategies.

iSupport was developed by the WHO for global implementation and therefore includes guidelines for translation and cultural adaptation of the intervention. Internet interventions are a promising channel to prevent or treat mental health conditions of relatives and other unpaid carers who face greater risk of experiencing mental health problems themselves [41]. iSupport may increase unpaid carers' worldwide accessibility to the support they need through the internet. An advantage of the intervention is that it is flexible and carers can decide which lessons they want to complete. Another advantage is that it can be provided with no or minimal professional support. This enables upscaling of the intervention without high costs. It might fit into a stepped-care model, in which only the carers who need more support are stepped up to face-to-face interventions. Additionally, family and other unpaid carers go through different stages during the course of dementia; their needs and preferences for training and support may substantially vary accordingly [42,43]. iSupport contributes to enriching and completing a continuum of interventions addressing the needs of carers in the Netherlands. This continuum should cover interventions from face-to-face to online interventions as well as guided to self-help interventions and everything in between.

The fact that the intervention is offered with minimal support might not only be a strength but also a weakness. It might lead to higher dropout rates. A review on the treatment adherence of online interventions carried out in 2008 [44] shows that in some trials participants never accessed the interventions tested, while others used them inconsistently. We try to minimize that risk by providing personalized automated feedback in iSupport as well as via periodic contact with e-coaches and the option to consult the e-coach more frequently. Hopefully, this encourages carers to continue with the intervention.

To the best of our knowledge, this is the first randomized trial for a minimally guided online intervention focusing on mental health outcomes for family and other unpaid carers of people with dementia in the Netherlands. This will provide valuable information for the Netherlands, but it will also contribute to the evidence for the use of iSupport at a global scale. An RCT of the Indian version of iSupport began in 2017 [19], and it is expected that more adaptations of iSupport will be completed worldwide in the future. We will test the effect of the intervention on different types of outcomes. Our study will try to overcome the possible challenges of RCTs of minimally guided online interventions, for example, by including personalized automated feedback. With our online and offline recruitment procedure, we expect to find a heterogeneous group of carers. Finally, the inclusion of a waiting list control group will allow all participants to benefit from the online tool.

In conclusion, using a two-arm RCT, our study will provide valuable information about the effectiveness of a minimally guided online intervention tool on participants by comparing outcomes with a waiting list control group. If the results of this study are satisfactory, iSupport may be a valuable response to an existing demand of carers for support in the Netherlands.

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Authors' Contributions

Conception and design of this study was carried out by ACP-B, AMP, AK, and AvS. Drafting of the article was carried out by ACP-B, AMP, AK, and AvS. Critical revision of the article for important intellectual content was carried out by AMP, AK, RMD, and AvS. Final approval of the version to be published was given by ACP-B, AMP, AK, RMD, and AvS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the European Commission.
[PDF File (Adobe PDF File), 96 KB - resprot_v8i10e14106_app1.pdf]

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Abbreviations

AD8: Ascertain Dementia 8-item informant questionnaire
ADQ: Approaches to Dementia Questionnaire
AN: Alzheimer Nederland
CBT: cognitive behavioral therapy
CES-D: Centre for Epidemiological Studies Depression scale
CONSORT: Consolidation Standards of Reporting Trials
HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale
INDUCT: Interdisciplinary Network for Dementia Using Current Technology
ITN: Innovative Training Network
N/A: not applicable
PMS: Pearlin Mastery Scale
PSS: Perceived Stress Scale
RCT: randomized controlled trial
RIS: relational self-efficacy, instrumental self-efficacy, and self-soothing efficacy
SSCQ: Short Sense of Competence Questionnaire
SUS: System Usability Scale
T0: baseline assessment
T1: 3-month follow-up assessment
T2: 6-month follow-up assessment
WHO: World Health Organization
ZBI: Zarit Burden Interview

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Protocol

Integrated Care Delivery for HIV Prevention and Treatment in Adolescent Girls and Young Women in Zambia: Protocol for a Cluster-Randomized Controlled Trial

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Abstract

Background: Among countries in sub-Saharan Africa, Zambia has one of the highest incidences of HIV. Adolescent girls and young women (AGYW) are a particularly affected group because of their social and economic vulnerability.

Objective: The goal of this study is to test a multilevel package of interventions at the community and health system levels in Zambia in order to connect AGYW with a source of regular care, which will in turn allow for sustainable, successful implementation of regular HIV testing and adherence to antiretroviral treatment.

Methods: We will adapt prior tools to create the SHIELD (Support for HIV Integrated Education, Linkages to Care, and Destigmatization) intervention to educate and empower Zambian AGYW of 10-24 years of age and their families and to create community-based youth clubs to foster peer support. We will also develop integrated wellness care clinics to offer a youth-friendly environment that provides tailored clinical services. We will perform formative research, including focus groups and in-depth interviews, among AGYW, caregivers, and stakeholders to help inform the development and tailoring of the interventions. A cluster-randomized controlled trial will be implemented in Lusaka, with six clinic catchment areas randomized into three groups: zones with integrated wellness care clinics and SHIELD intervention, zones with only SHIELD intervention, and control zones with no intervention. We will assess HIV testing among the HIV-negative or unknown (HIV-/u) cohort, and retention in care along with viral load suppression will be evaluated in the HIV-positive (HIV+) cohort. We will use in-depth interviews and surveys to collect staff and stakeholder feedback after the trial. Cost-effectiveness of the interventions and return-on-investment impacts will be quantified using a microsimulation model.

Results: Interim results are expected in 2021, and the final results are expected in 2022. If this multilevel intervention is successful in establishing a comprehensive care continuum for HIV-affected AGYW, the Zambian Ministry of Health may advocate for expansion to additional settings to support national scale-up.

Conclusions: This integrated service delivery model can also be a platform to implement additional preventive services, so HIV-/u and HIV+ AGYW can receive comprehensive, integrated services.

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International Registered Report Identifier (IRRID): PRR1-10.2196/15314

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KEYWORDS

HIV; prevention; treatment; Zambia; adolescent girls and young women

Introduction

Zambia is experiencing one of the highest incidences of HIV in the world, and adolescent girls and young women (AGYW) are a particularly affected group because of their social and economic vulnerability [1,2]. Approximately 5% of girls aged 15-19 years and 11% of young women aged 20-24 years are living with HIV in Zambia, with about 14,000 new infections among AGYW annually [1,3,4]. HIV counseling and testing are the key entry point for many HIV prevention interventions and essential for early linkages to HIV treatment [2]. With optimal use of antiretroviral therapy (ART), early diagnosis can reduce transmission to others and improve health outcomes [5-7].

The latest Zambian estimates indicate that only 42% of youth aged 15-24 years know their HIV status, 78% of those diagnosed with HIV are in treatment, and 71% of those in treatment have achieved viral suppression, resulting in a community viral load suppression (at the population level) of less than one-third of the total [8]. Evidence indicates that girls have less-comprehensive HIV knowledge than boys; face gender norms that increase their susceptibility, such as the view that women should never refuse sex with their husbands; and lack access to sexual and reproductive health services to support their reproductive rights [9,10].

The Zambian government prioritizes HIV services for adolescents and encourages evaluation of new models of care delivery to support “test and start” guidelines. Zambia has introduced comprehensive sexuality education, which is meant to be integrated in school curriculums, and is in the early stages of initiating facility-based ART adherence clubs [11]. To spearhead further progress, the government is interested in evaluating new models of HIV testing and treatment. Under the new “test and treat” guidelines [12], linkage to HIV care and retention in care are crucial to the success of ART treatment. A recent systematic review investigating the acceptability of HIV counseling and testing in children and youth aged 5-19 years in sub-Saharan Africa reported that provider-initiated testing and counseling achieved the highest acceptability (86%), followed by home-based HIV counseling and testing (84.9%) and school-linked HIV counseling and testing (60.4%) [13]. There is also some evidence that locating testing and care services within the same facility can improve care linkage and ART initiation [14-16]. Additional evidence is required on whether provider-initiated HIV counseling and testing in an adolescent-friendly, clinic-based setting that is colocated with HIV services can increase HIV testing and improve linkages to HIV treatment among AGYW.

Individual and interpersonal factors such as self-efficacy and social support are key facilitators of HIV testing and ART adherence among AGYW [17]. The transitions from child to teenager to young adult are crucial developmental phases that require age-appropriate interventions [17]. Training tools such as the Stepping Stones program and the Adolescent Girl Empowerment Program (AGEP) are proven to improve self-efficacy and increase HIV knowledge [18-21]. Additionally, during adolescence, both family support and peer influence are important [22,23]. Youth clubs are an important venue to help young people establish friendships and social bonds to support optimal HIV prevention and treatment behaviors [24].

Prior studies and initiatives have attempted to provide youth-friendly services through adolescent ART clinics that offer a range of services, but these clinics have faced challenges because of the stigma associated with HIV and the fear of privacy loss [25-27]. To address this gap, we are developing and testing an integrated wellness care delivery model that targets all HIV-affected AGYW, including those who are HIV-negative or whose status is unknown (HIV-/u) and those who are HIV-positive (HIV+). We will adapt the successful Zambian cervical cancer screening program, which provides a range of services to older women with and without HIV, to offer tailored services to AGYW [28,29]. The availability of the human papillomavirus (HPV) vaccine, which is targeted at AGYW (ages 10-24 years included in this study) and well-accepted in Zambia [30,31], provides an ideal opportunity to address the dual burden of HIV and cervical cancer. The integrated wellness care clinic will offer HIV testing, HIV treatment (in coordination with HIV clinic and dispensary in the same facility), HPV vaccination, and other HIV and sexual and reproductive health care services. Because AGYW experience individual and interpersonal barriers in seeking HIV and sexual and reproductive health services, we will also include a community-based behavioral intervention for AGYW and their families that is specifically tailored to the development stage of the AGYW.

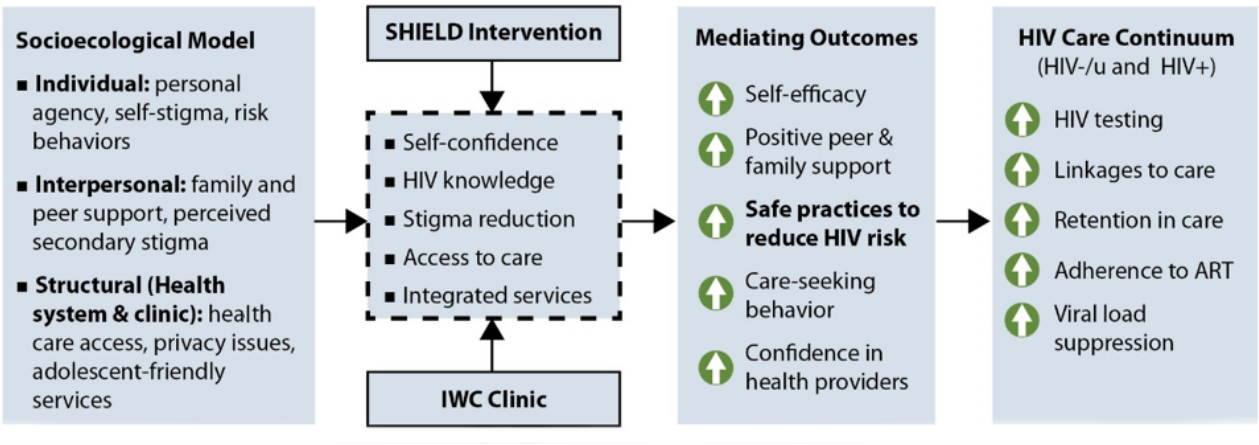
The overall goal of this study is to develop and test a multilevel package of interventions to connect AGYW in Zambia with a source of regular care, which will in turn provide a sustainable, successful implementation of regular HIV testing and support for linkage to care, retention in care, and adherence to antiviral treatment. This approach will avoid siloes and create a comprehensive HIV care continuum with a holistic, integrated health care delivery approach, which is recommended by the Zambian Ministry of Health guidelines for treatment and prevention of HIV [5].

Methods

Summary

To meet the overall goal, we will adapt prior tools to create the SHIELD (Support for HIV Integrated Education, Linkages to care, and Destigmatization) intervention to educate and empower AGYW and their families and to create community-based youth clubs to foster peer support. We will also create the adolescent-friendly integrated wellness care clinics to offer integrated services targeted at AGYW. The theoretical framework, based on the socioecological model, is presented in Figure 1. We will test the hypothesis that the combination of integrated wellness care clinics and age-appropriate SHIELD interventions for AGYW and their families will increase HIV testing, retention in care, and viral load suppression compared to the current standard-of-care clinical services with or without the SHIELD intervention.

Figure 1. Conceptual framework for creating a comprehensive care continuum for HIV-affected adolescent girls and young women. HIV-/u: HIV-negative or unknown; SHIELD: Support for HIV Integrated Education, Linkages to Care, and Destigmatization; IWC: integrated wellness care; ART: antiretroviral therapy.



Interventions

Support for HIV Integrated Education, Linkages to Care, and Destigmatization Intervention

The SHIELD intervention is based on social cognitive theory, which posits that positive behavior change requires knowledge and skills to increase behavioral capability, self-efficacy to increase the belief that one can achieve the desired outcomes, and social support to provide positive reinforcement and develop positive outcomes expectations [32]. We will develop a modular-based program for AGYW that increases their knowledge, skills, and self-efficacy to seek care. We also will develop an education program for family members to increase social support for AGYW. Intervention content for both AGYW and families will be tailored for five distinct groups to reflect AGYW's development stage and HIV status. The groups include ages 10-12, 13-15, and 16-20 years for HIV-/u AGYW, and ages 16-20 and 21-24 years for AGYW living with HIV. Modules will be adapted based on formative research (focus group and in-depth interviews) using existing evidence-based interventions such as Stepping Stones [20,21] and Families Matter! [33,34]. Modules will address HIV prevention and treatment, general wellness and sexual and reproductive health, approaches to combat stigma and discrimination, and skills for better communication and include new content on health service availability and access to increase self-efficacy in seeking health care services. In addition to the education modules, we will establish youth clubs for the five distinct groups by adapting those created for the AGEP initiative and other similar programs [18,19]. Youth clubs will be facilitated by peer navigators, who are AGYW aged 16-24 years and have been trained in participant confidentiality, AGYW rights, basic counseling skills, sexual and reproductive health, HIV continuum of care, processes of referral and linkages for health services, recruitment strategies, and study aims.

Integrated Wellness Care Clinic Intervention

Integrated wellness care clinics will be created where AGYW can receive sexual and reproductive health care services, including HIV testing and treatment, family planning, sexually transmitted disease screening and treatment, and HPV vaccination. Integrated wellness care clinics will be established in existing government health facilities and will follow the model of the cervical cancer screening clinics that have been embedded within government facilities to provide comprehensive services to women [28,29]. Standard operating procedures (SOPs) will be developed, covering HIV, HPV vaccination, and sexual and reproductive health clinical guidelines specific to AGYW; care pathways mapped out for common problems or conditions; procedures to maintain patient privacy; quality assurance checklists; and details on documentation and data capture (preprogramed computer tablets will be used to enter study data). We will also map out the physical structure and layout of the room for the integrated wellness care to ensure ergonomics in patient care processes and offer privacy for physical exams and counseling. We will explore the best options for placement of the integrated wellness care clinic within the health facilities with the use of at least two rooms: one devoted to the intake process and another to medical examinations. To accommodate AGYW, who are generally not available to attend clinics during work or school hours, the integrated wellness care operational hours will include early morning, late evening, and weekend hours.

Integrated wellness care clinic and health center staff will be trained to ensure that staff offer holistic HIV and sexual and reproductive health services, including family planning, sexually transmitted infection diagnosis and treatment, and condom promotion, in a nonjudgmental and friendly manner. This training will include learning the SOPs, gaining hands-on experience by shadowing nurses at the same facility to understand clinic procedures, and receiving antistigma training. We will conduct a pilot study with 25 AGYW drawn from the study sampling cohort to finalize the SOPs.

Cohort Recruitment and Sampling Frame

To select the study sites, we will identify six health centers or clinics that provide HIV services and cervical cancer screening in the Lusaka district. To establish a sampling frame from which to recruit participants for the randomized trial (described below), cohorts of HIV-/u and HIV+ AGYW will be recruited based on residence in the catchment areas of these clinics, which are the zones immediately surrounding the clinics. To avoid potential

cross-contamination, we will select clinic zones that are not contiguous. All the clinics will be located within the greater Lusaka area, and each government clinic draws patients from specific catchment areas surrounding the clinic. We will therefore focus on ensuring that the clinic catchment areas do not overlap and are not adjacent to each other. We will conduct a discrete choice experiment concurrently with the recruitment of the AGYW for the sampling frame. The discrete choice experiment will be conducted to systematically evaluate preferences for HIV clinical care services (this information will also be used to further tailor the integrated wellness care clinic package of interventions, as appropriate). AGYW will be asked to choose among scenarios with varying combinations of key attributes relevant to HIV and other clinical care services (for example, service availability, wait time, operating hours, provider type, and protection of privacy). A key design consideration for the discrete choice experiment is to allow for both group-level and individual-level differences. We plan to perform subanalyses by age group and HIV status to assess differences by developmental stage and have ensured that the sample size of 1000 HIV-/u AGYW (approximately 330 in three age groups) and 800 HIV+ AGYW (approximately 400 in two age groups) will be adequate to perform the planned analysis [35-37]. The sample sizes required for the follow-on randomization were also taken into account for determining the size of the initial HIV-/u and HIV+ cohorts to establish the sampling frame.

To identify the HIV-/u cohort, we will map out each neighborhood and households within the clinic catchment area with the assistance of the local neighborhood health committees, the community liaisons attached to the clinics, and the outreach staff from the cervical cancer program. Peer navigators will visit each household, beginning with residential areas closest to the clinics, to identify eligible AGYW and recruit them to participate in the study. Participants will be notified of their rights, that questions regarding HIV status will be discussed, and that their refusal to participate will not affect their access to health care or other services. All AGYW aged ≥18 years will provide written informed consent in their preferred language, and written parental consent will be obtained for participants under 18 years of age, followed by written assent from these minors. We will include one AGYW per household and enroll AGYW on a continual basis until we reach our desired enrollment targets. Participants in the HIV-/u cohort must be female, be 10-20 years of age, and self-report their HIV status as negative or unknown ("unknown" defined as no HIV testing within the past 6 months).

We have selected the age group of 10-20 years because this is the highest-priority cohort and because prevention interventions are best delivered early to establish healthy behavior patterns before HIV exposure. Additional inclusion criteria include the participant not being pregnant, not suspecting she is pregnant, and not expressing a desire to become pregnant in the next 18 months; willing to sign a release for medical records (to obtain clinic data on service use); plans to reside in the same location for the next 18 months; and not been part of the other planned formative research activities. We will exclude pregnant AGYW because their motivations and health-seeking behaviors are likely to change during pregnancy, they require specialized antenatal care, and they are not eligible for the HPV vaccine that will be offered to the integrated wellness care clinic participants. All pregnant AGYW identified during the study will be offered assistance for obtaining care at appropriate antenatal clinics. We will recruit 160-170 adolescent girls from each clinic catchment area, with equal numbers in the 10-12, 13-15, and 16-20 year age ranges, for a total of 1000 girls.

For the HIV+ cohort, to maintain confidentially, we will request that health providers and community outreach staff at target clinics, along with staff from community-based testing centers, approach eligible HIV+ AGYW who reside in the clinic catchment area (identified through patient record review) to seek their consent to be contacted by the research team about the study. This preconsent process has been designed to be concise with as little detail of the study as possible to protect HIV+ participants' confidentiality. Individuals administering the preconsent process will be able to give participants an overview of the study along with information on the methodology and research ethics. Should HIV+ AGYW accept, members of the research staff will contact them and administer a more detailed consent form to help inform the potential participants' decision to participate. The use of community outreach staff will allow us to target AGYW who are HIV+ but not receiving treatment in addition to those who are actively engaged in care. Those who voluntarily indicate that they are HIV+ during recruitment of the HIV-/u cohort will also be given the opportunity to enroll in the HIV+ cohort if they are eligible. Participants who are female, 16-24 years of age, and diagnosed with HIV within the past 3 years (to target relatively recently diagnosed AGYW at the time of recruitment) will be eligible. Those who receive an HIV+ diagnosis during our 3-month recruitment time frame will also be included. In Zambia, sexual acts with adolescents younger than 16 years, even if consensual, are considered criminal. Given the possible negative repercussions that AGYW may experience should they be reported and our desire to maintain a trusting relationship with the communities that we wish to serve, we will not recruit adolescent girls aged ≤15 years for the HIV+ cohort. We will enroll 800 HIV+ AGYW, targeting a similar number (130-140) from each clinic zone with equal representation among those aged 16-20 years and 21-24 years. The additional inclusion criteria listed above will also be applied to the HIV+ cohort.

The systematic approach for establishing the sampling frame will provide discrete, nonduplicated individuals (the participant list will be updated daily); reduce selection bias by ensuring a more representative sampling for the cluster-randomized trial; and, if necessary, allow for adjustments in the random selection process, so that AGYW cohorts are similar across randomization arms.

Randomized Controlled Trial

Cluster Randomization Study Design and Interventions

The selected zones and their respective clinics will be randomized into three groups: zones with integrated wellness care clinics and SHIELD intervention (integrated wellness care+SHIELD), zones with only SHIELD intervention (SHIELD only), and control zones with no intervention at the clinic or

community levels (usual care). This division will allow us to assess the impact of offering integrated wellness care clinics coupled with the SHIELD intervention compared with the standard of care and whether a similar impact can be achieved with control clinics when the SHIELD intervention is offered in the community. Figure 2 shows the trial design and group sample sizes. Figure 3 shows the study periods and timeline for the trial initiation, postallocation, and analysis. The SHIELD intervention, as described earlier, will begin with training sessions for AGYW and their families. This will be followed by peer navigator–facilitated youth clubs that will meet twice a month during the 12-month study time frame. Two peer navigators will be assigned to each clinic zone with the SHIELD intervention, and one peer navigator each will be assigned to the two control clinic zones to assist with data collection and follow-up activities. To avoid cross-contamination, each peer navigator will remain in their assigned zones for the study duration. The peer navigators in the zones with integrated wellness care clinics will also serve as community liaisons to support clinic-community linkages. The primary endpoint for the HIV-/u cohort is the proportion with any HIV testing at 12 months. For the HIV+ cohort, we plan to assess two primary endpoints: retention in care, measured as proportion with at least one visit during each 3-month period (over the 12-month follow-up), and viral load suppression measured as the proportion with undetectable viral load at 12 months. The secondary endpoints are the proportion with a decrease in HIV risk behavior, repeat HIV testing (each 6-month period), HIV infections diagnosed through HIV counseling and testing, linkages to HIV care, and adherence to ART. Table 1 presents the endpoint definitions and biological, self-report, and clinic audit measures collected at 6- and 12-month follow-ups. To assess the impact of the SHIELD intervention on the mediating outcomes, we will collect data from both AGYW and their caregivers (one family member identified by AGYW) from across all six clinic zones at baseline and at 6- and 12-month follow-ups. Additionally, we will track the health care service use by collecting clinic data at all six clinic sites. Information will be obtained from the clinical records at baseline and during the 6- and 12-month follow-ups by using prespecified abstraction forms. Specially trained staff will perform biological data collection, which will include HIV testing at 12 months for the HIV-/u group, viral load testing at 12 months for the HIV+ group, and pregnancy testing for both groups at baseline and 12 months.

Figure 2. Experimental design and sample sizes. AGYW: adolescent girls and young women; SHIELD: Support for HIV Integrated Education, Linkages to Care, and Destigmatization; IWC: integrated wellness care.

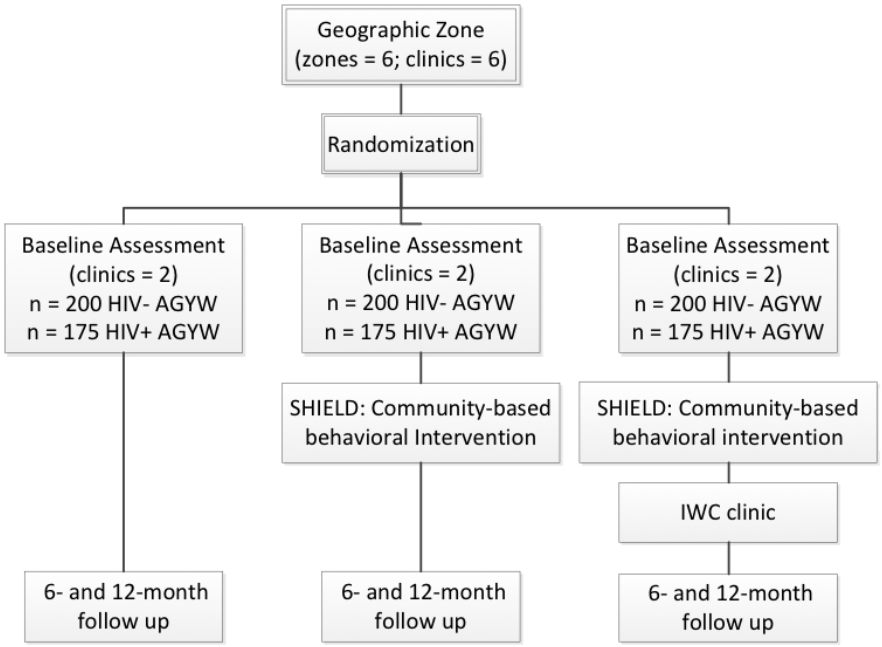


Figure 3. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flow diagram of the cluster-randomized controlled trial. IWC: integrated wellness care; SHIELD: Support for HIV Integrated Education, Linkages to Care, and Destigmatization.

	Establish Sampling Frame	Randomization & Baseline Data Collection	Postallocation		Close-out
TIMEPOINT (approximate time frames)	*November 2019 - April 2020*	*October 2020 - March 2021*	*6-month follow-up (April 2021 – October 2021)*	*12-month follow-up (October 2021 – March 2022)*	*June 2022*
ENROLLMENT:					
Eligibility screen	✓	✓			
Informed consent		✓			
Allocation		✓			
INTERVENTIONS:					
SHIELD			←	→	
SHIELD + IWC			←	→	
ASSESSMENTS:					
Questionnaire		✓	✓	✓	
Clinic audit			✓	✓	
Biological tests			✓	✓	
Provider			✓	✓	
ANALYSIS:					
Cost-effectiveness, budget impact, and policy implications					✓

Table 1. Measures and source at baseline, 6 months, and 12 months.

Constructs/measures	Instrument and specification	Source	Cohort
Primary and secondary endpoints—HIV care continuum and HIV risk behavior			
HIV testing: proportion tested for HIV in the past 6 and 12 mo	Abstraction tool (serologic HCT[a]) and self-report confirmed via clinic audit; repeat HCT at 6-month intervals will be assessed	Clinic audit, self-report	HIV-/u[b]; 6 mo and 12 mo
HIV early detection: proportion with HIV identified through voluntary testing	All participants will be tested to determine HIV status (rapid finger prick and follow-up per Zambian guidelines)	Biological	HIV-/u; 12 mo
Linkage to care: proportion enrolled at an HIV clinic in ≤30 days; *ART initiated* in ≤*90 days*	Measured as days from testing HIV positive or from baseline when not on treatment (HIV+ but not on ART[c])	Clinic audit	HIV-/u, HIV+[d]; 6 mo and 12 mo
Retention in HIV care: proportion with at least one visit every 3 months	Prespecified abstraction tool to capture any HIV care–related visits over a 12-month period (clinic or dispensary visits)	Clinic audit	HIV+; 6 mo and 12 mo
Adherence to ART: proportion filling prescriptions at least every 3 months	3-month supply of ART medications recommended by Zambian guidelines	Clinic audit	HIV+; 6 mo and 12 mo
Viral load suppression: proportion with undetectable viral load	HIV plasma viral load tests using the Roche platform	Biological	HIV+; 6 mo and 12 mo
HIV risk behavior: proportion with delay in first intercourse, reduction in sexual partners, increases in condom use	Demographic and health survey and AGEP[e] instrument (measures will be based on previous studies by grant team, including AGEP)	Self-report	HIV-/u; baseline, 6 mo, and 12 mo
Mediating outcomes, SHIELD[f] intervention dose, and clinic-based services			
Self-efficacy	Measurement scale developed and tested for the AGEP	Self-report	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
Social support (AGYW[g] report on family and peer interaction)	Medical Outcomes Study instrument previously used in Zambia [38]; AGEP PN[h] and youth club feedback instrument	Self-report	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
Mental health	Strengths and Difficulties Questionnaire, youth version [39]	Self-report	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
HIV stigma, gender-based violence	AGEP instrument	Self-report	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
Unintended pregnancy	Tested at baseline and 12 mo	Urine test	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
Education modules (AGYW and family)	Number of modules completed	Study database	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
Youth club attendance	Number and proportion of meetings attended	Study database	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
Caregiver assessment	Parent Strengths and Difficulties Questionnaire and survey on AGYW support (to be developed)	Self-report	HIV-/u and HIV+; baseline, 6 mo, and 12 mo (unless otherwise specified)
HPV[i] vaccination	Proportion receiving 1, 2, or 3 doses (IWC[j] clinic only)	Clinic audit	HIV-/u and HIV+; 6 mo and 12 mo

Constructs/measures	Instrument and specification	Source	Cohort
Number of clinic visits	Proportion with visits at 6 mo and 12 mo; total number of visits	Clinic audit	HIV-/u and HIV+; 6 mo and 12 mo
Sexual and reproductive health services provided	Family planning, sexually transmitted diseases, and condoms	Clinic audit	HIV-/u and HIV+; 6 mo and 12 mo
PNs and clinic staff feedback on AGYW HIV care			
PNs	PN feedback instrument (to be developed)	Self-report	Baseline, 6 mo, and 12 mo
Clinic staff attitudes and feedback	10 staff interviewed at each clinic; modified Nyblade instrument	Self-report	Baseline, 6 mo, and 12 mo
Baseline data for AGYW			
Demographics and socioeconomic status	AGEP baseline instrument	Self-report	All AGYW

[a]HCT: HIV counseling and testing.

[b]HIV-/u: HIV-negative/unknown.

[c]ART: antiretroviral therapy.

[d]HIV+: HIV-positive.

[e]AGEP: Adolescent Girl Empowerment Program.

[f]SHIELD: Support for HIV Integrated Education, Linkages to Care, and Destigmatization.

[g]AGYW: adolescent girls and young women.

[h]PN: peer navigator.

[i]HPV: human papillomavirus.

[j]IWC: integrated wellness care.

Selection of Adolescent Girls and Young Women and Sample Size Determination

In each clinic zone, we will use stratified random sampling, using age-group strata drawn from the sampling frame previously established, to select AGYW for the HIV-/u and HIV+ study cohorts (integrated wellness care pilot study participants will be excluded). The selection criteria will remain the same as the sampling frame recruitment. Those who become pregnant (confirmed by urine test at intake) will be excluded, and those who become HIV seropositive (self-reported) will be assigned to the HIV+ cohort if they meet the age criteria; we will oversample by 20% in each age subgroup to account for ineligibility. Because we will have an established sampling frame, we will review the AGYW characteristics in each clinic zone to determine whether a more complex selection process is warranted to control for potential differences in characteristics between AGYW. The sample size was calculated assuming conventional specifications (power=.80, alpha=.05, two-sided tests) with an intracluster correlation coefficient (ICC) close to 1 and based on the primary endpoints. The justification for using an ICC of ~1 is supported by our knowledge of the six selected local government clinics and their surrounding communities (clusters). The clinics all provide the same standardized clinical services in similar facilities and serve a generally homogeneous catchment population of low-income individuals. Additionally, our analysis will be conducted at the individual level, which will allow us to control for any unanticipated variation at the individual or cluster level.

The sample sizes allow for the detection of a 15-percentage point improvement in the primary endpoints, which is our minimum threshold to consider the intervention to be successful. For the HIV-/u cohort, the current rate of HIV testing is estimated to be about 40%. With a sample size of 200 per randomization groups, we will be able to detect a 13%-14% difference. The grant team achieved a 90% retention rate at 12 months in a recent study of AGYW [18]; with a loss of 10% of the cohort during our follow-up in this study, we will still have the statistical power for a minimum detectable difference of 15% in HIV testing. For the HIV+ cohort, both retention in care and viral load suppression is estimated to be 70%-75% among AGYW. With a sample size of 175 per randomization group, we will be able to detect a minimum difference of 15% even with a 10% loss to follow-up. We will enroll 600 HIV-/u AGYW (10-20 years of age) and 525 HIV+ AGYW (16-24 years of age) across the three randomization groups.

Hypotheses on Intervention Effect

We will test the following hypotheses:

- HIV-/u AGYW from zones randomized to integrated wellness care+SHIELD will have higher HIV testing than AGYW in zones randomized to SHIELD only or usual care.
- HIV+ AGYW from zones randomized to integrated wellness care+SHIELD will have higher retention in care and viral load suppression than AGYW in zones randomized to SHIELD only or usual care.
- HIV+ AGYW from zones randomized to integrated wellness care+SHIELD will receive more timely linkages to care than AGYW in zones randomized to SHIELD only or usual care.
- AGYW from zones randomized to integrated wellness care + SHIELD or SHIELD only will have improved self-efficacy and social support and reduced HIV risk behaviors compared with AGYW from zones randomized to usual care.

Analysis of Hypotheses

The testing of the primary hypotheses will be done by intent to treat, and we will examine the effects across the three randomization groups. Given the need to consider the influence of the cluster randomization by zone, we will use generalized estimating equation models to estimate the effects of the randomization groups and will assess the need to apply small sample correction using approaches suggested by the National Institutes of Health Care Systems Collaboratory Biostatistics and Design Core [40]. If the Hausman assumption of correlation between the random and fixed effects is violated, then we will include fixed effects representing cluster identification. We will adjust for baseline covariates, including sociodemographic factors and behavioral risks, should the initial descriptive analyses suggest differences in the distribution of these factors across study randomization groups. We will also explore the use of propensity scores to control for systematic differences between the groups. In further analyses, we will examine the potential mediating and moderating roles of key behavioral, social, and structural factors hypothesized to influence HIV testing and adherence along the HIV care continuum (eg, social support and self-efficacy), as shown in Figure 1. The specific measures, along with the instruments and specifications, that will be used are shown in Table 1. We will test the "dose" of the SHIELD training received as a covariate in these models.

Secondary analysis will follow the same approach. As appropriate, we will perform analyses separately or pooled together for the HIV+ and HIV-/u cohorts. A key aspect of interest in this study is the developmental stage of the AGYW; using age as a proxy in our multivariate analysis, we will determine the differential effect of the integrated wellness care clinic and SHIELD intervention on outcomes reported by age group and HIV status. In subsequent analyses, we will also consider both medium-term outcomes (within the first 6 months after study enrollment) and longer-term outcomes (within the first 12 months after study enrollment). Additionally, for measures where we have baseline, 6-month, and 12-month follow-up data (for example, self-efficacy and other mediating outcomes for AGYW and caregiver), we will perform difference-in-difference analysis, which will allow for comparisons between and across the study arms. We will also report all mediating factors, caregiver outcomes, and integrated wellness care clinic utilization metrics stratified by age and HIV status to facilitate subgroup analysis. Importantly, the changes along the HIV care cascade, including HIV testing, linkage to care, retention in care, ART adherence, and viral load suppression, will be documented to identify potential differential impacts of the interventions. This analysis is critical to assist in further tailoring the SHIELD training and integrated wellness care clinic services.

Cost-Effectiveness, Budget Impact, and Policy Implications

We will use a previously validated instrument, The Cost Assessment Tool [41], to collect resource use information on the interventions. Our main goal is to estimate the implementation cost of the integrated wellness care and the SHIELD interventions from the program perspective, but we will also derive the start-up costs related to developing the interventions to inform future adaption of these interventions to other settings. We will estimate labor hours by prospectively tracking time spent by each project staff member on a predefined set of activities (individuals will report their time monthly) and use hourly wage to calculate costs. We will also document the expenditure on nonlabor resources. Using standard economics methodology [42,43], we will explore economies of scale that can be achieved during scale-up. The cost information, along with the impact of effectiveness of the integrated wellness care and SHIELD interventions, will be used as inputs in previously validated models [44]. We will evaluate the tradeoff, or return on investment, between investing in HIV prevention and lowering HIV treatment cost over the long term. The usual care (base case) will be compared to the long-term effectiveness of including the SHIELD community-based interventions with and without the integrated wellness care clinic-based intervention to address barriers along the continuum of care. We will report the projected decrease in HIV incidence, the projected increase in community-level viral load suppression, and the incremental cost per quality-adjusted life years. We will conduct policy simulations to assess the impact of scaling up the interventions to the population level; perform sensitivity analysis, varying the range of effectiveness and cost estimates; and generate potential best- and worst-case scenarios. We will create tornado and spider diagrams to display this uncertainty assessments graphically to policy makers. This cost-effectiveness analysis will be complemented by a budget analysis, which will identify the annual financial outlays that will be required to implement the interventions during various phases in the scale-up process.

Results

Data collection from formative research will be completed in March 2020. The cluster-randomized trial is expected to begin in 2020. Analysis will be performed to test the hypotheses indicated, and additional analysis will be conducted on the cost-effectiveness, budget impacts, and policy implications of the interventions. Results of this study will be shared with the research community and the public at large through conference presentations and publication in peer-reviewed journals. Results are expected in mid-2023.

Discussion

Limitations and Approaches to Minimize Bias

First, although cluster randomization reduces contamination across study arms, it increases the risk that clinics and individuals in each arm may differ at baseline. The unique feature of this study is that we will create a sampling frame and will therefore be able to assess individual-level baseline differences before randomization. The sampling frame will also allow us to adjust our sampling process or *a priori* include propensity score weighting methods during analysis to match individuals with similar characteristics. Additionally, through our planned situational analysis, we will explore clinic characteristics to select clinics that are similar.

Second, data could be missing because of nonresponse as well as study attrition. All AGYW will be assigned to a peer navigator who will ensure regular contact with the AGYW during the study period. We will also employ rigorous field data collection practices, including training data collectors, developing protocols, and monitoring fidelity on a continual basis. Using this approach, on the basis of a recent study among Zambian AGYW by the study team, we expect that retention will be 90% over the 12-month follow-up period [18]. Furthermore, we will address any missing data by including demographic covariates that will serve as proxies for dropout and by conducting sensitivity analyses.

Policy Implications

The knowledge gained in this study will address a critical gap in our understanding of effective public health interventions to improve engagement of AGYW along the HIV care continuum. It will test community- and clinic-based interventions to address key barriers to engagement in care at the individual, interpersonal, and clinic levels including HIV knowledge, stigma, social support, and the need for youth-friendly services. If successful, the proposed interventions will improve HIV testing, retention in care, and treatment adherence among AGYW and will contribute to meeting the 90-90-90 and 95-95-95 targets, reducing secondary transmission and improving the quality of life of AGYW affected by HIV. Successful implementation of this multilevel intervention to establish a comprehensive care continuum for HIV-affected AGYW will provide a strong evidence base for expanding integrated HIV and sexual and reproductive health services for AGYW both nationally and within sub-Saharan Africa.

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Authors' Contributions

SS and PE conceptualized the study, identified data elements, identified analytic methods, and wrote the protocol. SR, MM, and MZ contributed to the conceptualization of the study, supported the development of the methods, and reviewed the protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the NIH.
[PDF File (Adobe PDF File)154 KB - resprot_v8i9e15314_app1.pdf]

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Abbreviations

AGEP: Adolescent Girl Empowerment Program
AGYW: adolescent girls and young women
ART: antiretroviral therapy
HCT: HIV counseling and testing
HIV-/u: HIV-negative or unknown
HIV+: HIV-positive
HPV: human papillomavirus
ICC: intracluster correlation coefficient
IWC: integrated wellness care
PN: peer navigator
SHIELD: Support for HIV Integrated Education, Linkages to Care, and Destigmatization
SOP: standard operating procedure

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Protocol

Weight Loss After Stroke Through an Intensive Lifestyle Intervention (Group Lifestyle Balance-Cerebrovascular Accident): Protocol for a Randomized Controlled Trial

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Abstract

Background: Weight gain can be a consequence of stroke, or cerebrovascular accident (CVA), because of impaired mobility, behavioral and emotional disorders, and sensory losses. Weight gain increases the patient's risk of recurrent stroke and chronic diseases, such as diabetes, metabolic syndrome, and pulmonary and heart disease. Approaches to weight loss in this population are lacking, although necessary because of the unique physiological and cognitive needs of persons after a stroke. Evidence shows that intensive behavioral therapy interventions that address both physical activity and diet offer the greatest potential for weight loss. The Group Lifestyle Balance (GLB) intervention is a 12-month, evidence-based weight loss program that has been used extensively with the general population; this program was modified to meet the needs of people who have had a stroke (GLB-CVA).

Objective: This randomized controlled trial (RCT) aims to examine the efficacy of the GLB-CVA on weight and secondary outcomes, compared with that of a waitlist control group.

Methods: This RCT will enroll and randomize 64 patients over an 18-month period.

Results: Currently, 51 people are waitlisted, with 23 out of 51 screened and 16 out of 23 eligible.

Conclusions: It is anticipated that the findings from this RCT will contribute to the evidence base regarding weight loss strategies for people living with stroke.

Clinical Trial: ClinicalTrials.gov NCT03873467; https://clinicaltrials.gov/ct2/show/NCT03873467

(JMIR Res Protoc 2019;8(10):e14338) doi:10.2196/14338

KEYWORDS

cerebrovascular accident; physical activity; eating; weight loss; rehabilitation

Introduction

Background

Stroke, or cerebrovascular accident (CVA), is a serious public health issue because of its high incidence, high cost of care, and increased risk of morbidity and mortality [1]. Projections show that by 2030, an additional 3.4 million people aged >18 years will have had a stroke, which is a 20.5% increase in prevalence from 2012 [2]. Estimates indicate that about one-third of stroke survivors have excessive weight, causing them to be overweight or obese (body mass index or BMI ≥25 kg/m^2) [3]. Weight gain significantly restricts functioning and independence and greatly increases the risk of chronic diseases, such as diabetes, metabolic syndrome, pulmonary disease, heart disease, and recurrent stroke [4,5].

There is a high prevalence of weight gain and obesity after stroke, as people's physical activity and healthy eating behaviors are negatively impacted [3]. This may be because of a

combination of personal (eg, low motivation and lack of social support) and environmental factors (eg, lack of transportation, high cost of specialized programming, and lack of education from health care providers) [6]. Yet, increased physical activity and healthy dietary habits are recognized approaches to reduce the risk of comorbidities, such as obesity, hypertension, diabetes, recurrent stroke, and heart disease [7]. However, there is a lack of evidence-based approaches to weight loss for people after stroke [8]. Most currently available evidence-based weight loss programs were developed and tested with samples from the general population, with *disability* often used as an exclusion criterion [9,10]. Thus, the appropriateness of these programs to meet the unique needs of people who have had a stroke is unknown.

The Group Lifestyle Balance (GLB) program is a 12-month self-management intervention that has been shown to result in weight loss and reduce the risk for type 2 diabetes through improved physical activity and healthy eating behaviors [11-15]. Although the GLB has been used extensively with the general population [16,17], no study has been conducted specifically for people who have had a stroke. This protocol describes a randomized controlled trial (RCT) that will assess the efficacy of the GLB program that has been modified with input of stroke survivors (GLB-CVA). The GLB-CVA program will be compared with a waitlist control group. This protocol followed the standard protocol items: recommendations for interventional trials checklist to report relevant clinical trial details, as recommended by the Enhancing the Quality and Transparency of Health Research Network.

Objectives

Aim 1

Aim 1 of this study is to examine adherence to GLB-CVA intervention participation.

- *Hypothesis:* Intervention participants will attend at least 70% (15/22) of the weekly and monthly group-based sessions [18].

Aim 2

Aim 2 of this study is to conduct an RCT to examine the efficacy of the GLB-CVA on primary and secondary outcomes in the intervention group, compared with the waitlist control group at 3 and 6 months from baseline.

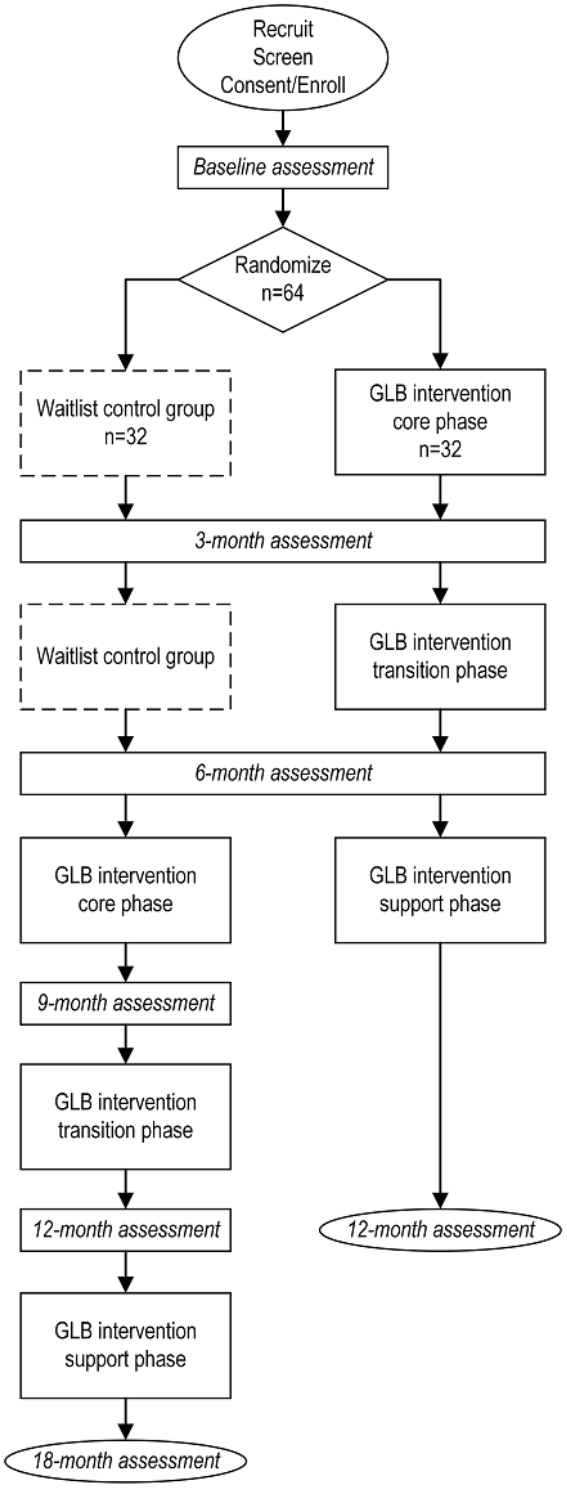
- *Hypothesis 2.1:* The intervention group will demonstrate statistically significant improvements in our primary (weight) and secondary outcomes (activity assessed with accelerometers, waist and arm circumference, blood pressure, hemoglobin A_{1c}, fasting glucose and lipid panel, 8-year diabetes risk, functional measures, self-report measures of physical activity and healthy eating, executive function, perceived social support, self-rated abilities for health behavior practices, pain interference, sleep disturbance, habits, and quality of life) when compared with the waitlist control group at 3 and 6 months.
- *Hypothesis 2.2:* Combined intervention data from both groups will demonstrate significant improvements in primary and secondary outcomes after 3, 6, and 12 months.

Methods

Study Design

The design is a single-phase, assessor-blinded, and waitlist-controlled RCT. Human subjects approval has been received by the Baylor Scott and White Research Institute Institutional Review Board (018-714); the study has been registered on ClinicalTrials.gov (NCT03873467). The intervention design and timeline are outlined in Figure 1.

Figure 1. Enrollment and assessment schedule. GLB: Group Lifestyle Balance.



Study Setting

Study procedures will be completed at Baylor Scott and White Institute for Rehabilitation, a large rehabilitation hospital in an urban setting in the southwestern United States.

Participants and Recruitment

The primary sources of recruitment will be Baylor Scott and White Institute for Rehabilitation and community agencies in the Dallas–Fort Worth metroplex. Recruitment will be completed by trained interventionists who are members of the research team, and approaches include in-person visits to community organizations and stroke support groups, flyers, calls, and physician referrals, with a snowball technique for further recruitment. Recruitment will occur over a 4- to 6-month period to ensure that the target sample size is reached.

Eligibility

Interested participants will contact or be contacted by the research team using information provided on approved study flyers. An eligibility screener will be completed telephonically with the following inclusion criteria: (1) BMI ≥25 kg/m^2, (2) aged 18 to 85 years, (3) all types of stroke, (4) at least 12 months after stroke, and (5) physician approval to be physically active and make dietary changes. Exclusion criteria are as follows: (1) low cognitive function (<10 on the Cognistat) [19], (2) residing in a hospital, acute rehab setting, or skilled nursing facility, (3) preexisting diagnosis of an eating disorder, (4) pregnancy, (5) taking medication for diabetes, or (6) not fluent in English language. Before the completion of study procedures, informed consent will be obtained by trained research personnel in a private room at Baylor Scott and White Institute for Rehabilitation.

Intervention

The GLB intervention promotes self-management of a healthy lifestyle based on the tenets of Social Cognitive Theory [20] and the Health Belief Model [21]. The GLB program facilitates individual engagement in health behavior change and is completed in a group setting [11-15]. Data from previous GLB trials have shown 5% to 7% weight loss in a variety of settings, including community centers, churches, worksites, and health care systems [13,16,22-28]. The goal for participants is to reach 150 min of physical activity following the American Heart Association's (AHA) recommendations and follow dietary guidelines by the United States Department of Agriculture. The GLB program comprises 22 sessions over 12 months, including 12 weekly core program sessions, 4 transition phase sessions, and 6 support sessions (see Multimedia Appendix 1). GLB program materials are made available to the public under the Creative Commons licensing agreement through the Diabetes and Prevention Support Center at the University of Pittsburgh that developed the GLB program.

The GLB curriculum was adapted based on the recommendations from an advisory board of 29 key stakeholders, including stroke survivors, caregivers, clinicians (eg, physicians, therapists, registered dieticians, and neuropsychologists), community partners (eg, AHA and support groups), and researchers, with specific consideration for individuals with stroke (GLB-CVA). The advisory board met to review and discuss relevant changes to the existing curriculum during a 1-day meeting and were compensated US $100 for their time. The recommended modifications were then made by the study team and approved by the Diabetes and Prevention Support Center at the University of Pittsburgh. Modifications included (1) reorganizing and refocusing the content to reflect the importance of healthy behaviors on heart health and prevent recurrent stroke, (2) reducing the volume of content to focus on 2 to 3 main points at each session, (3) involving care partner in the sessions to provide physical and emotional support, (4) developing stroke-specific handouts on weight loss barriers and healthy lifestyle importance, (5) creating and locating handouts and weblinks to modify physical activity and adaptive cooking, and (6) including guest lectures by experts in the field (eg, physical therapist and dietitian). The GLB-CVA intervention will be delivered by trained GLB lifestyle coaches at Baylor Scott and White Institute for Rehabilitation. Training was completed at either the University of Pittsburgh's Lifestyle Coach Training Workshop or Master Training Center at Baylor Scott and White Health and Wellness Institute. Both sites have recognition by the Centers for Disease Control and Prevention (CDC) as official GLB training centers.

Outcome Measures

Participants will complete assessments at 4 time points over the course of the yearlong intervention, including baseline, 3, 6, and 12 months. The waitlist control group will complete 2 additional assessment periods that serve as data for comparison in the RCT before they undergo the 12-month intervention. Demographic data collected will include the following: type of stroke, severity of disability (Modified Rankin Scale [29]), current age, date of stroke, sex, parental history of diabetes, race and ethnicity, education level, premorbid history of mental illness, marital and relationship status, diagnosed medical conditions, previous and present smoking and cigarettes per day, alcohol consumption and drinks per week, residence status and zip code, annual household income category, pre- and current stroke insurance type, pre- and current employment status, prestroke and current weight, height, and resting metabolic rate with MedGem. The primary and secondary outcomes are outlined in Multimedia Appendix 2 [30-49]. Participants will be compensated US $25 for their participation at each study time point. Assessments will be completed by a data collector who is trained as a medical assistant and phlebotomist and has completed Modified Rankin Scale training for previous stroke studies.

Sample Size

For the proposed study, 64 participants (32 per group) will be enrolled. The sample size was calculated to ensure that we have sufficient power for our analyses on the primary outcome (weight). Previous GLB studies with the general population have demonstrated weight loss over time (median d=0.99 at 3 months, 0.91 at 6 months, and 0.74 at 12 months) [15-18]. Results also indicated a maximum attrition rate of 16%, 23%, and 33% at 3, 6, and 12 months, respectively. Thus, a sample size of 64 will allow a power of greater than 90% to detect a conservatively assumed group difference of 4% in weight change (95% power). In the event of 33% attrition, we will achieve 83% to 87% power to detect these differences.

Allocation

Participants will be assigned to the experimental GLB-CVA or waitlist control groups using computer-generated random numbers in Microsoft Excel. Individuals in the waitlist control will be placed on a waiting list and receive the intervention after a 6-month period. To ensure an equal distribution between groups, block randomization will be used with blocks of sizes 4 and 6. Randomly mixing block sizes will reduce the study coordinator's ability to predict the last assignment of each block. The randomization list will be generated by the biostatistician, with results contained in sealed envelopes labeled with study identification numbers. After a participant is enrolled in the study, a study coordinator will select the assigned envelope to

reveal the participant's group. Owing to the type of intervention, it is not practical to blind study participants to group assignment. However, to minimize assessor bias, outcome assessments will be conducted by a coordinator who (1) is blinded to group assignment, (2) is not included in study team meetings, (3) has a script to remind participants at the beginning of each assessment to maintain blinding, and (4) has a process for recording unblinding.

Data Management, Quality Assurance, and Exclusion of Bias

All nonelectronic source documents will be kept in a locked storage cabinet in the Baylor Scott and White Institute for Rehabilitation research office. Case report forms and all outcomes data will be inputted into REDCap (Vanderbilt, TN), a Health Insurance Portability and Accountability Act–compliant (21 Code of Federal Regulation Part 11) secure Web-based program, by trained study staff. All electronic data will be stored and maintained on a secure server and disposed in accordance with current federal guidelines.

Data management activities will occur quarterly and include data quality checks and verification, as well as internal logic checks (eg, outlier values and internal inconsistencies). Of the participant files, 10% will be audited for source document and data entry review. Cross-tabulation checks using SAS will also be applied to the data. Data will be stored and backed up periodically by the biostatistician on the secure server. Descriptive statistics will be prepared and included into quarterly reports to ensure the quality of data and study progress. The principal investigator will provide oversight on all data entry and proper data monitoring and audit procedures.

Statistical Methods

To examine adherence to the GLB-CVA intervention (Aim 1), univariate analysis will be used to summarize session attendance to determine if it reaches the hypothesized rate of at least 70% (15/22). An RCT will be completed to examine the efficacy of the GLB-CVA on primary and secondary outcomes in the intervention group compared with the waitlist control group at 3, 6, and 12 months from baseline. General mixed modeling analysis will be conducted for the primary and secondary outcomes to assess initial and sustained impacts of the adapted GLB-CVA intervention. More specifically, individual growth models will be evaluated for linear and nonlinear change from baseline to 3, 6, and 12 months (level 1, time effects), overall group difference (level 2, group effect), and group difference in change (cross-level, time-by-group interaction effect; Hypothesis 2.1). Models will be adjusted for demographic variables (eg, age, gender, ethnicity, and disability severity using the Modified Rankin Scale), particularly if they are imbalanced after randomization, thereby providing more accurate estimates of the intervention impacts.

Separate growth models for change from baseline to 12 months will be fitted within both groups combined (time effects only; Hypothesis 2.2). Data will include missing observations resulting from either attrition or nonresponse. Intent-to-treat analysis will use restricted maximum likelihood estimation, which can produce unbiased estimates with incomplete data. In addition, sensitivity analysis will utilize iterative Monte Carlo Markov Chain multiple imputation for missing data. All selected variables will be used in the imputation process, allowing for greater recovery of the missing data. All analyses will be performed using SAS 9.4.

Results

We currently have 51 people on the waitlist. Of these, 23 have been screened, and 16 of the 23 are eligible and scheduled for baseline assessments. The intervention is expected to start in the summer of 2019.

Discussion

The aim of our study is to examine the efficacy of the GLB-CVA on the weight as well as health and function of people who have had a stroke. As the fourth leading cause of disease burden globally, stroke and the resultant comorbidities (ie, hypertension, obesity, and diabetes) present a significant public health challenge, and interventions are therefore needed [50]. A combination of health behaviors (physical activity, nonsmoking, moderate alcohol intake, and adequate vitamin C intake) is known to reduce the incidence of stroke 2-fold [51]. Moreover, any lifestyle intervention attempting to improve health in people with stroke should include, as a primary focus, management of weight, blood pressure, cholesterol, and glucose [52]. Nonpharmacological interventions (ie, physical activity and healthy eating) are necessary, in addition to medication, to address these modifiable risk factors. However, a recent scoping review of the physical activity and stroke literature [53] found only 3 lifestyle intervention trials [54-56] that incorporated both physical activity and healthy eating strategies. Although the studies had short-term benefits (9-24 weeks) on mobility, dietary behaviors (salt intake), and metabolic factors (blood pressure and cholesterol), the longitudinal effects on weight, health, and function were not documented. As such, the GLB program was chosen because of data consistently demonstrating 5% to 7% weight loss, evidence of success in other disability populations [57] and programmatic flexibility to address the unique health and function needs of people post-CVA.

Although physical activity and healthy eating are foundational to evidence-based weight loss programs and recognized to reduce the risk of hypertension, obesity, diabetes, and heart disease [58-60], after stroke, people encounter significant challenges to maintaining a healthy lifestyle. Common barriers following stroke include personal (eg, low motivation and physical impairment) and environmental factors (eg, lack of accessible facility and no transport) [6,61-64]. These barriers, in addition to others (eg, lack of social support and limited financial resources), reduce the ability of people who have had a stroke to participate in community-based health and wellness programs, further increasing their risk of developing comorbidities (eg, obesity, diabetes, and heart disease). To adapt a healthy lifestyle intervention to meet the unique needs of people who have had a stroke, modifications must account for common barriers to healthy lifestyle behaviors and address frequent health risks after stroke.

The GLB-CVA program was modified from the original evidence-based curriculum, with inputs from 29 advisory board members, to meet the specific needs of people with stroke. This modified curriculum addresses the unique needs of people with stroke by incorporating the inclusion of care partners, stroke-specific handouts on weight loss barriers, reduced content to 2 to 3 main points for each session, reorganization and refocus on the importance of healthy lifestyle on stroke prevention and heart health, weblinks, and guest lecturers for stroke-specific modifications to physical activity and adaptive cooking. Findings from this RCT are expected to establish a strong evidence-based approach to weight loss among people after stroke that is scalable into community settings throughout the nation.

Upon completion of this RCT, all GLB-CVA materials will be made accessible to the public at no charge through the Diabetes Prevention and Support Center at the University of Pittsburgh. The GLB program was selected because of the fact that it is acknowledged by the CDC-National Diabetes Prevention Recognition Program (CDC-DPRP) as an evidence-based lifestyle program. In addition, Centers for Medicare and Medicaid Services recently included the GLB into the Medicare payment program, allowing individuals to be reimbursed for participation [65]. The primary goal of this RCT is to attain full recognition by the CDC-DPRP and achieve reimbursement from the Centers for Medicare and Medicaid Services for people with stroke living in the community.

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Authors' Contributions

SD was responsible for study inception, design, oversight, and the first draft of the paper. CS and KFG contributed to the scientific merit and design of the study. MB provided sample size calculations and statistical support. EM and SC established study operations and recruitment. All authors have read and contributed to this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Group Lifestyle Balance curriculum.
[PDF File (Adobe PDF File)137 KB - resprot_v8i10e14338_app1.pdf]

Multimedia Appendix 2
Outcome measures for Group Lifestyle Balance-Cerebrovascular Accident project.
[PDF File (Adobe PDF File)108 KB - resprot_v8i10e14338_app2.pdf]

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Abbreviations

ACL: Administration for Community Living
AHA: American Heart Association
BMI: body mass index
CDC: Centers for Disease Control and Prevention
CDC-DPRP: Centers for Disease Control and Prevention-National Diabetes Prevention Recognition Program
CVA: cerebrovascular accident
GLB: Group Lifestyle Balance
HHS: Health and Human Services
NIDILRR: National Institute on Disability, Independent Living, and Rehabilitation Research
RCT: randomized controlled trial

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Protocol

Deaf Adults' Health Literacy and Access to Health Information: Protocol for a Multicenter Mixed Methods Study

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Abstract

Background: Deaf American Sign Language (ASL) users often struggle with limited health literacy compared with their hearing peers. However, the mechanisms driving limited health literacy and how this may impact access to and understanding of health information for Deaf individuals have not been determined. Deaf individuals are more likely than hearing individuals to use the internet, yet they continue to report significant barriers to health information. This study presents an opportunity to identify key targets that impact information access for a largely marginalized population.

Objective: This study aims to elucidate the role of information marginalization on health literacy in Deaf ASL users and to better understand the mechanisms of health literacy in this population for the purpose of identifying viable targets for future health literacy interventions.

Methods: This is an exploratory mixed methods study to identify predictors and moderators of health literacy in the Deaf population. These predictors of health literacy will be used to inform the second step that qualitatively explains the findings, including how Deaf individuals access and understand Web-based health information. Multiple interviewer- and computer-based instruments underwent translation and adaptation, from English to ASL, to make them accessible for the Deaf participants in our study. A planned sample of 450 Deaf ASL users and 450 hearing native English speakers, aged 18 to 70 years, will be recruited from 3 partnering sites: Rochester, NY; Flint, MI; and Chicago, IL. These individuals will participate in a single data collection visit. A subset of participants (approximately 30) with key characteristics of interest will be invited for a second data collection visit to observe and inquire more about their ability to directly access, navigate, and comprehend Web-based health information. The study will help assess how the ways health literacy and information are visualized may differ between Deaf individuals and hearing individuals. The study will also survey participants' ownership and use of computer and mobile devices and their level of Web-based information use, including health information.

Results: Adaptation and translation of protocols and instruments have been completed and are now in use for the study. Recruitment is underway and will continue until late 2020. Results from this study will be used to provide a guide on how to structure Web-based health information in a way that maximizes accessibility and improves health literacy for Deaf individuals.

Conclusions: The results from this mixed methods proposal will advance what is known about health literacy and health information accessibility for Deaf individuals. This innovative study will generate rich data on how to formulate health information and health literacy interventions more accurately to take advantage of visual learning skills.

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KEYWORDS

deaf; hearing loss; consumer health information; health literacy

Introduction

Background

Deaf American Sign Language (ASL) users are nearly 7 times more likely than their hearing peers to have inadequate health literacy [1]. Deaf ASL users (henceforth, Deaf) rarely receive language concordant health care services and are at highest risk for miscommunication with their health care providers. Deaf individuals understand less than 30% of what is being said through lipreading [2,3]. Furthermore, prose literacy poses a challenge for Deaf individuals; the average Deaf individual reads English at the fifth- to sixth-grade level [1,4-7]. The use of interpreters is the standard of care for Deaf ASL users, yet they are infrequently provided [8]. The majority of Deaf individuals (approximately 95%) have hearing family members who do not sign. Thus, many experience the *dinner table* syndrome, where they have encountered years at the dinner table watching close family members and friends converse with each other while being unable to understand what is being said, depriving them of incidental learning opportunities that many hearing individuals take for granted [9]. The loss of incidental learning opportunities and information marginalization for Deaf individuals occurs daily in a broad range of work, schools, friends, families, government, media, and health care contexts [1]. Many Deaf ASL users learn language, health information, and even culture via peers rather than family [10] and struggle to identify and correct misinformation [11]. Due to this communication-depleted milieu, inadequate health literacy may be an important cause of the lower level of health-related knowledge and worse health outcomes that have been observed among Deaf individuals.

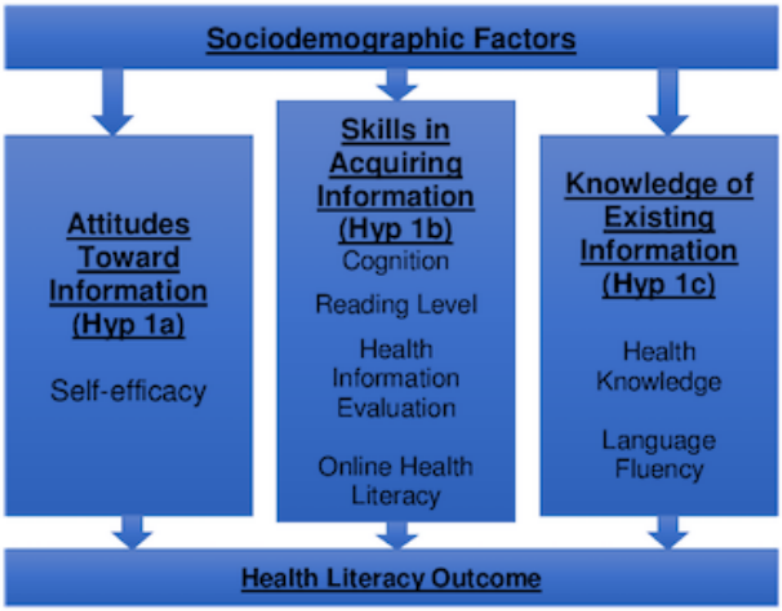
Deaf individuals, because of their social and language marginalization, appear to use Web-based health information more frequently than the general population [12,13]. However, it is unclear if Deaf individuals access Web-based health information or other information sources effectively and what degree of impact this may have on their health literacy. In the general population, there is evidence that health literacy impacts mortality, yet the connection remains inconsistent when looking at other clinical outcomes [14]. In multiple studies, positive associations with both health literacy and electronic health (eHealth) literacy and improved quality of life, better use of health care services, and improved health behaviors among individuals with different types of health conditions were demonstrated [15-17]. An area of concern is that disadvantaged populations, notably those with chronic health conditions or disabilities, may struggle with eHealth literacy. This may promote additional inequalities in their ability for Web-based health information to influence positive outcomes such as self-management of health care needs in these individuals. What is needed is to understand how to design technology and Web-based health information in a way that may benefit these types of consumers [18,19]. As Deaf individuals communicate through a visual language, the proposed study provides an opportunity to determine optimal visual-based information sources, providing another avenue to help those with lower health literacy. Individuals with low health literacy struggle in locating relevant Web-based health information and may fixate on irrelevant aspects of displayed information [20]. Such a phenomenon may be important for populations such as the Deaf who are dependent on visual mechanisms for communication and for overcoming information gaps.

This study describes the methods used to study the role of information marginalization on health literacy for Deaf individuals. The authors describe approaches for instrument adaptations and measures applicable for Deaf individuals who use ASL. Finally, a description of the unique aspects of our proposed data collection method is shared in this paper. The research objectives are two-fold: (1) to elucidate the role of information marginalization on health literacy in Deaf signers and (2) to better understand the mechanisms of health literacy in this population for the purpose of identifying viable targets for future health literacy intervention development.

Study's Theoretical Framework

There are few mechanism-based studies in health literacy research and none involving Deaf and hard of hearing individuals. A review of the literature helped with developing ideal conceptual models to guide the project's proposal. The authors modified and created a hybrid of 3 widely used health literacy and diffusion theory conceptual models: (1) the attitudes, skills, and knowledge (ASK) model [21], (2) the health literacy model [22], and (3) the diffusion theory [23] for Deaf individuals. Figure 1 illustrates constructs that are relevant to health literacy and health-related information. Sociodemographics, cognition, educational achievement including reading skills and task performances, and general health knowledge have all been shown to be related to each other with respect to health literacy in the general population [21]. Additional aspects of health literacy that need to be better understood in the Deaf community include the role of attitudes (ie, the feeling and trust one has toward information), skills (ie, the tools that allow one to seek, obtain, and understand information), and knowledge (ie, demonstrates comprehension). It is hypothesized that the factors outlined in the model are key elements of health literacy for Deaf individuals. As a result, our Deaf Health Literacy conceptual model regarding information includes 3 main concepts that lead to health outcomes and are being used in this study to inform data collection and analysis.

Figure 1. Deaf health literacy conceptual model for information.



To help explain how and why certain characteristics may impact health literacy, including ability to access, navigate, and understand Web-based health information, a qualitative interview along with thematic analysis will be performed. This will explain the interrelation in outcomes of interest (eg, what characteristics are associated with adequate health literacy), intermediary outcomes (eg, what backgrounds, skills, and contextual factors allow for better navigational ability on the Web), and personal conditions that need to be explored further (eg, cognitive issues).

Methods

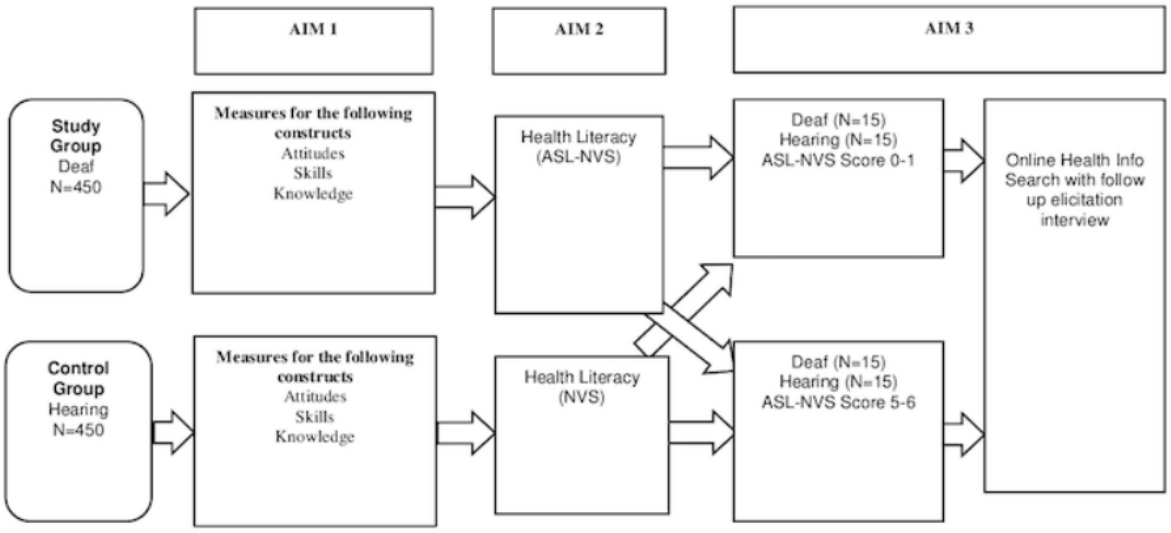
Overview

For this study, there are 3 proposed aims. Aim 1 is to evaluate differences in ASK, regarding health information for both Deaf signers and hearing English speakers. Aim 2 plans to assess hearing status as an effect modifier of the association between health literacy and ASK with health information. Aim 3 will qualitatively assess the impact of health information accessibility and patterns of use on health literacy with one-on-one elicitation interviews. This will be based on actual Web-based health information searches for 4 clinical vignettes using an observed task fulfillment experiment as a prompt. The goal of this aim is to explore differences with Web-based health information search ability and health knowledge acquisition in a subsample of Deaf and hearing individuals recruited from aims 1 and 2. The University of Michigan institutional review board (IRB) approved the study and provides coordination with the following IRBs: Sinai Hospital, Rochester Insitute of Technology, and Hurley Medical Center (HMC). The study is also registered at the ClinicalTrials.gov under ID NCT03093779.

Study Design

The study uses an explanatory sequential mixed methods design [24] with extensive quantitative data collection procedures to identify predictors and moderators of health literacy. We will first conduct a cross-sectional study to collect predictors of health literacy. These predictors of health literacy will be used to inform the subsequent phase of qualitative assessment. For example, elicitation interviews with selected participants returning for the second data collection visit will be used to help explain the quantitative results and to help elucidate how Deaf individuals access and understand Web-based health information. The study will use a stratified sampling approach to invite participants of certain characteristics to return for further data collection. Characteristics of interest will be based on quantitative analyses that show significant associations between health literacy and any of the measured variables (eg, educational attainment, age, or reading literacy). Approximately 15 Deaf and 15 hearing participants with inadequate health literacy and another 15 Deaf and 15 hearing participants with adequate health literacy will return for a second visit to conduct a task performance on a desktop computer and participate in a follow-up interview designed to learn more about their decision making and preferences. The return visit will involve a qualitative assessment using elicitation interviews to help explain any of the quantitative results. The goal is to learn how and why Deaf individuals access and understand health information (Figure 2) and how this may differ from hearing individuals.

Figure 2. Overall study design. ASL-NVS: American sign language-newest vital sign.



The project uses a community advisory board (CAB) with representation from study sites. The CAB is designed to provide community oversight and guidance on the research protocol development and interpretation of findings. The board consists of 6 Deaf community members, 2 from each of the research data collection sites.

Study Setting and Participants

The study will recruit 450 Deaf and 450 hearing participants at 3 primary data collection sites. The sites include HMC at Flint, MI (selected because of its diverse Deaf patient population, along with previous research collaborations with the University of Michigan); The National Technical Institute of the Deaf (NTID), which is housed at the Rochester Institute of Technology in Rochester, NY (selected because of NTID's experience in research and Rochester's highly educated Deaf community); and The Sinai Deaf Health program in Chicago, IL (selected because of its long-standing commitment to Deaf health education and research and its minority community).

Recruitment

Recruitment occurs at each site through the use of flyers, email listserves, social media postings and vlogs (video-based blogs), and community outreach. Once a potential participant is deemed eligible, a research staff educates him or her on the study, and if interested in proceeding, an in-person research visit is scheduled. The informed consent is reviewed and signed at the in-person visit before proceeding with the study. The research staff who worked with the Deaf participants are fluent in ASL.

Eligibility Criteria

To be eligible, study participants must be aged at least 18 years. For the Deaf study group, eligible Deaf participants must identify themselves as Deaf and communicate primarily in ASL. For the hearing comparison group, the hearing study participants also must be aged at least 18 years but self-report normal hearing and communicate in spoken English (ie, English monolinguals). Participants will be excluded if they have any cognitive impairments (eg, because of dementia, delirium, or intoxication), inability to consent to the study, or limited vision.

Sample Size

To detect differences between correlations at 1% level of significance with 80% power, based on a one-sided Z-test of comparison of Fisher Z-transformed correlations, we plan to recruit 450 participants in each group that will allow us to detect a minimum difference of 20%. The sample size is more than adequate in detecting the differences between the groups with respect to the accessibility, acquisition, and attitude measures in aim 1 as well as to assess deafness as an effect modifier of the association between health literacy and ASK with health information.

Measures

The constructs outlined in the Deaf Health Literacy conceptual model will be measured through a collection of chosen tools (see Table 1). These tools were selected primarily because of their accessibility (prior use with past projects involving Deaf participants) and their key constructs that they measure. There were several tools that required translation and adaptation before they could be used in the study. A translation work group (TWG) was formed for this purpose. ASL is a language with its own rules of semantics and syntax similar to other languages.

Table 1. Key variables and their measures.

Key variables	Measures	Defintion
Attitudes		
Self-efficacy	One's belief in one's ability to succeed in specific situations.	Self-efficacy for information seeking [26].
Skills		
Cognition	Ability to process information, metacognition, and behavioral regulation, which all are important for learning and social behavior	Kaufman Brief Intelligence Test, Second Edition (assesses nonverbal cognition), and the Color Trails Test (assesses executive function) [27] provide standard scores. Both have been used extensively in Deaf populations [28,29].
Reading literacy	Level of reading proficiency	reading grade level from the Test of Silent Contextual Reading Fluency, Second Edition [30]. This instrument is visual and provides a suitable tool for both Deaf and hearing populations.
Electronic health (eHealth) literacy	Ability to seek out, find, evaluate and appraise, integrate, and apply what is obtained in an electronic or Web-based environment to solving a health problem.	eHealth literacy Scale (validated measure of Web-based and eHealth literacy) [31]. Adapted further for the Deaf ASL[a] users that includes whether Web-based information is accessible in ASL.
Visualization of health information	Visualization patterns of the presented health information.	Actual through eye tracking software, which assesses the visualization of health-related information on 4 health topics [20,32].
Knowledge		
Health knowledge	Knowledge of cardiovascular health.	Wagner et al's cardiovascular health knowledge measure [33].
Language fluency	Level of expressive and receptive language proficiency.	(1) ASL-SRT[b] [34] and (2) Speaking Grammar Subtest of the Test of Adolescent and Adult Language, Third Edition [35]. Both will assess reception and expressive fluency in both ASL and spoken English. The ASL-SRT has been used extensively in Deaf populations [36,37].

[a]ASL: American Sign Language.

[b]ASL-SRT: American Sign Language Sentence Reproduction Test.

The shape, placement, and movement of hands as well as facial expressions and body movements all play important parts in conveying important information. There is no written form of ASL, so the use of *ASL gloss* is a way to keep note of how the ASL concepts should be signed to convey the meaning of the question or instructions accurately. Furthermore, the use of gloss has to do with the fact that the target language may not have equivalent words to represent the original language. The majority of the instruments were already available in ASL before the study's funding, but there was translation and adaptation work needed for the following instruments: eHealth literacy Scale (eHEALS; 8 questions), Pew Research Center's *Health Online Survey* questions related to online technology and information use (41 questions) [25], certain sociodemographic questions, cardiovascular knowledge assessment (25 questions), and self-efficacy instrument (3 questions).

The TWG consisted of the principal investigator (PI), a faculty experienced in translation of research instruments for Deaf individuals, 1 ASL interpreter skilled in medical terminology, and 3 native Deaf signers experienced with translation work. This translational workgroup approach was successful in the adaption of prior measures (eg, American Sign Language-Newest Vital Sign, ASL-NVS) [1]. All TWG team members are bilingually fluent in English and ASL, including expertise within their content area or translation work. Moreover, the team members have Deaf cultural issues as they are members of the Deaf community. The TWG members, including Deaf and hearing individuals, worked collaboratively in small groups to prepare, review, and perform quality checks. In addition to multiple intrateam reviews during the translation and filming process (videos used for internal reviews and back-translation steps), external reviewers, who were not members of the translation team, provided an added layer of review and validation to ensure the quality and integrity of the work. A final blind back-translation from the ASL videos back to the English text was done by 2 bilingual Deaf experts (not involved with the TWG) to ensure translation accuracy. The above steps, including selection of the team, were done to establish appropriate language and cultural translations.

Health Literacy Assessment

The study will use an accessible and validated health literacy instrument for Deaf individuals that the PI derived from the Newest Vital Sign (referred to as the ASL-NVS) [38]. The ASL-NVS also offers other benefits as it assesses numeracy and reading literacy, has a short administration time with only 6 questions, and has been created and validated for other languages (eg, Spanish). The ASL-NVS is the first, and currently

only, health literacy instrument available for the Deaf population. The instrument is available online [39].

Attitudes Assessment

Self-Efficacy

The *Self-efficacy for Information Seeking* scale is based on a scaled 3-item questionnaire assessing beliefs about ability to effectively perform specific information-related behaviors, such as finding information about health, evaluating the accuracy of health information, and using the internet to find information [26].

Skills Assessments

Nonverbal Cognitive Ability

The *Kaufman Brief Intelligence Test, Second Edition* (KBIT2) [40], Matrices Subtest (nonverbal intelligence quotient [IQ]) is computed based on one's performance on a single multiple-choice subtest that does not require language skills. There are 46 items composed of several types of items involving visual stimuli, both meaningful (people and objects) and abstract (designs and symbols). All items require understanding of relationships among the stimuli and require the participant to point to the correct response. The KBIT2 nonverbal IQ has a 0.82 correlation with the Wechsler Adult Intelligence Scale, Third Edition, nonverbal composite [40]. This test has recently become commonly used in cognitive science and psycholinguistic studies that have included Deaf participants [21,22,29] to control for individual cognitive differences.

Executive Function Ability

The *Color Trails Test* (CTT) [27] is a measure of executive function abilities where participants are asked to rapidly connect numbered circles in sequence by alternating between pink and yellow circles [27]. The time to complete the task is recorded. The CTT has a test-retest reliability of 0.79 and has good factorial and criterion-related validity [27] with individuals with frontal lobe injuries. One of the coinvestigators (PCH) has used this test in cognitive science studies involving Deaf participants [28,29].

Reading Literacy

This will be assessed through the Test of Silent Contextual Reading Fluency, Second Edition [30]. This tool provides an efficient standardized literacy assessment for both Deaf and hearing participants.

Electronic Health Literacy

eHEALS was adapted to make it more culturally and linguistically appropriate for Deaf ASL users. The 8-item questionnaire inquires about the participants' knowledge, comfort, and perceived skills at finding, evaluating, and applying eHealth information to health problems [31]. An additional 41 questions derived from the Pew Research Center's *Health Online Survey* [25] related to online technology and information will assess the participant's level of information access and use. This also was expanded to inquire about ownership of computer and mobile-based devices.

Health Information Evaluation Skill

Actual behaviors will be assessed for each participant through the use of the eye tracking software (Tobii; Tobii Technology) on 4 standardized health topic pages (2 with a picture and 2 without a picture). Eye tracking technology will be used to observe their ability to visualize and understand standardized health information with and without pictures. For eye tracking, we will use the Tobii eye tracker and software for data collection on fixation duration and fixation count on the presented information and the visualization pattern on both websites. This eye tracker provides extremely detailed eye tracking metrics (in milliseconds), including fixation counts, visit duration, time to first fixation, and percentage of viewing time fixated/clicked on a certain area of interest. It also can be used in either static (eg, print) or dynamic (eg, video or website scrolling) to assess each participant's areas of interest.

Knowledge Assessments

Health Knowledge

A validated, general health knowledge test called the Heart Disease Fact Questionnaire [33] will be used. It assesses knowledge of cardiovascular health in a true/false/do not know questionnaire with 25 questions. There is a paucity of general health knowledge assessments that are validated. This tool is one of the few that provides a range of topics to assess participants' knowledge and has been used in a previous study involving Deaf individuals.

Language Fluency

As Deaf individuals reside in communities that use English as the *lingua franca* (or *de facto* language), they are frequently bilingual. Fluency will be assessed in both ASL and English for the Deaf participants. English will be assessed for the hearing participants. ASL fluency will be tested with the *American Sign Language Sentence Reproduction Test* (ASL-SRT) [34], which is a brief global measure of individuals' receptive and expressive ASL skills. Participants are required to watch videos of 20 ASL sentences and correctly reproduce the sentences after each one is presented. Correct reproductions are awarded 1 point, and the maximum total score is 20. ASL-SRT has been used in other cognitive science and psycholinguistic studies [36,37] and has been adapted to other signed languages. The ASL-SRT interrater reliability coefficient is 0.83, with an internal consistency (Cronbach alpha) of .88. CConstruct validity was established by illustrating that Deaf adults perform better on this test than Deaf children (P<.001; partial eta sq=.042) and native signers perform better than nonnative signers (P<.001; partial eta sq= 274). An equivalent and parallel test is available that assesses the receptive and expressive spoken English abilities that will be used for hearing participants. The test is called *Speaking Grammar Subtest of the Test of Adolescent and Adult Language, Third Edition* (TOEL3) [35], and has been widely used for language fluency assessments. The TOEL3 has internal consistency (Cronbach alpha) of .95, with test-retest reliability coefficient of 0.80.

Sociodemographic information will be based on an existing shortened version of the Behavioral Risk Factor Surveillance Systems [41]. This will be used to evaluate key demographic

information for each participant and adjust for covariates in health literacy. For Deaf participants, additional questions will be asked to provide information on the following: (1) presence of Deaf family members, (2) ownership of a hearing aid or cochlear implant, (3) hearing status with and without a hearing aid or cochlear implant, (4) onset of hearing status, (5) any cultural identity with their hearing status, (6) Deaf school attendance, and (7) socialization preferences based on hearing status (Deaf, hearing, or both). We will also perform a Shoebox Audiometry [42] on all participants to assess their unaided hearing levels (HLs) from (−)10 dB to 90 dB at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz for each ear. Shoebox is a leading tablet-based audiometer, which is a class 2 medical device registered and listed with the Food and Drug Administration. It offers a clinically validated, self-administered, automated testing platform optimized for use outside of a sound booth; can be completed in 5 min or less; and is completely configurable. HL will be defined by the standard greater than or equal to 25 dB average loss across the 4 frequencies in the better ear [43]. This will allow us to control for hearing loss variations among participants, especially because they may influence the level of access to information.

Procedures

Once the participants are eligible, the research team will schedule an in-person visit to review both the informed consent and administer the different measures. This was done in the same fashion at each performance site. The research staff review the consent form and the brief study information directly in the participant's preferred language (eg, ASL if Deaf). Once consent is obtained, the staff then proceeds with the data collection protocol. The measures are grouped into the following categories: (1) demographics/background information (includes Shoebox Audiometry), (2) interviewer-administered questionnaires (ie, cardiovascular knowledge assessment, self-efficacy, Web-based health information use, and e-literacy), (3) computer-administered measures (ASL-SRT, TOEL-3, and the ASL-NVS), (4) booklet testing (ie, CTT, KBIT2, and TOSCRF-2), and (5) Tobii eye tracker experiment. To avoid any ordering bias, the categories (except for the demographic/background information) are randomized to each participant (see Multimedia Appendix 1). The computer-generated randomization was completed before any participant recruitment. The counterbalance checklist designed with 4 blocks (A, B, C, and D) was randomly assigned to each participant (eg, 1 participant may get a checklist C that starts with booklet testing).

Procedures for Return Visit (for Those to Be Invited)

There will be 2 parts when the participant returns for their second visit (see Table 2). The first step will observe how participants search and acquire Web-based health information. This task performance will include 4 brief clinical vignettes (ie, pneumonia, deep vein thrombosis, migraines, and appendicitis) and multiple-choice answers will serve as a prompt. This will be given to all invited aim 3 participants to examine their abilities to search for health information on the Web and acquire health knowledge. Participants' query formulations, navigation patterns, cursor activity, total search times, and number and nature of websites accessed to address the clinical vignettes will be recorded and assessed through the use of the Tobii usability testing software already available in our facilities [44]. The data will include video footage of the participant (including eye movements and facial expression), websites visited, duration of page visited, and number of clicks and cursor activity. The use of the Tobii provides several benefits: (1) the tool provides real-time dual-screen recording and display of both the participant's actions online and webcam recordings of their facial expressions and eye movements; (2) the interviewer can watch the actions of the participant on the interviewer's computer screen through the use of the Tobii Pro Studio software program in real time; (3) the interviewer can tag different-colored annotations (eg, search queries, websites accessed, and challenges encountered) to the video data being recorded, which is visible on the time bar; (4) the tool can instantaneously compute summary statistics such as the total search time in seconds, the number of unique websites and pages visited, and the number and characteristics of queries issued for the interviewer to discuss with the participant; and (5) the interviewer can scroll quickly to the relevant time of the video to help the participant observe and remember their actions but, more importantly, allow for the interviewer to ask more detailed questions on how and why specific actions were chosen and the participant's thought process related to the online information. A figure demonstrating the different components and how it works can be accessed at Tobii website.

The recordings from the task performance above will serve as a prompt for the elicitation interview. It will help inform the subsequent qualitative assessment to help explain the quantitative results (of aims 1 and 2) and elucidate how and why Deaf individuals access and understand health information. Similarly, the same approach will be conducted with a subsample of hearing individuals. This will be done to provide robust comparisons. Video-based and semistructured qualitative assessments will be used to determine both how and why Deaf and hearing participants of different health literacy strata (inadequate and adequate; n=15 each) may differ in their performances with Web-based health information searches. The findings here will be used to help explain results from aims 1 and 2. The elicitation interview questions will be generated initially from the findings in aims 1 and 2 and complemented with additional questions following completion of the task performance on a computer. The interviewer will playback the dual-screen recording of the participant's actions to facilitate recall of his or her own actions and thoughts with each task undertaken. The interviewer will encourage the participant to make his/her thoughts transparent, that is, telling how and why the choices were made in a narrative format. The dual-screen recording with performance metrics will serve as stimulus material for the video elicitation interview. As the dialog between the interviewer and the participant will be in ASL (visual language), a separate external video camera will be used to record this interaction for later transcription. The interview will reveal the complex cognitive and decision-making processes that may occur with each individual, which are not adequately revealed in earlier statistical analysis. The incorporation of both steps provides better integration of the findings of all 3 aims and generates robust data to guide future intervention

development to address inadequate health literacy and information marginalization for Deaf populations. A strength of this step is the ability to explore contextual factors (ie, task- and user-oriented factors) that could not be explained with the first visit. As stated by a newer eHealth literacy model [45], these task- and user-oriented factors are important in their roles in the overall eHealth context. The proposed step will help examine how these intrapersonal and system-based factors may shape the Web-based health experience and abilities for both Deaf and hearing individuals.

Table 2. Aim 3 approaches.

Definition	Purpose	Approach	Data collection	Expected outcomes
Web-based health information navigation and comprehension (step 1)	To assess Web-based health information search ability, acquisition, and patterns	Use of Tobii video/online use recording software; 4 clinical vignettes with questions to prompt Web-based search	Navigation patterns of Deaf individuals; preferences of health websites, including search engines (n=15 Deaf and n=15 hearing for comparison); scoring on questions related to vignettes	Assess Web-based health information search ability of Deaf individuals (unknown); determine if Deaf individuals' health literacy determines the quality of the navigation and comprehension of the information (unknown); generate areas of weaknesses and strengths for interventions to focus (unknown)
Elicitation interviews (step 2)	To explain and expand the understanding of the findings demonstrated in aims 1 and 2	Use of elicitation interviews about video recordings of the participants and their Web-based searches	Explore how and why participants decided to use the websites they chose, including the types of queries and what aspects of the Web-based information was useful to them	Assess how Deaf individuals visualize and learn Web-based health information (unknown); determine the preferences of health information tools and dissemination (unknown) and understand why they have those preferences (unknown)

Statistical Analyses for Aim 1

Frequency statistics will be used to summarize categorical data, whereas means (SDs) were computed to describe continuous data. Correlations between main study variables will also be analyzed using Pearson r correlation coefficients. Differences between the Deaf and hearing participants in terms of ASK related to health information will be assessed using linear regression models. To control for the effects of demographic and physiological covariates on the dependent variables of ASK related to health information, sociodemographic (eg, race) and physiological factors (ie, hearing loss severity and laterality) will be entered in model 1 as potential confounding factors affecting each variable of interest. As we are primarily interested in the additional effects of ASK related to health information on health literacy and eHealth, predictor variables will be subsequently entered in model 2. Differences between the Deaf and hearing participants in terms of ASK related to health information will be assessed using linear regression models. The scales for each modality described in Table 1 will be used as a separate outcome with Deaf versus hearing as the primary covariate. A propensity-adjusted analysis will also be conducted with the propensities defined as the predicted probability of having adequate health literacy as a function of sociodemographic factors estimated through a logistic regression model. For observational data, the propensity-matched methods are often deemed to be a better alternative to the usual multiple linear regression controlling for potential confounders. Strata based on propensity quantiles will be used as a categorical covariate in the linear regression model. Furthermore, the variability across sites will be controlled for in the model. Usual model diagnostics will be performed, followed by corrective actions as necessary.

Statistical Analyses for Aim 2

The ASL-NVS and the English-NVS will be used to assess the health literacy score in both Deaf and hearing participants, respectively. The health literacy indicator (ASL-NVS) ranges in value from 0 to 6. To understand whether the association between health literacy and ASK related to health information differs between Deaf and hearing individuals, we shall compute in the Deaf and hearing groups Fisher Z-transformed partial correlations between health literacy and each of the constructs, adjusted for the socioeconomic factors and potential site differences. Subsequently, 2-sample Z-test of these correlations will be carried out for each construct. We shall supplement this analysis with a regression approach where health literacy will be regressed on the group and each of the constructs along with their interaction controlling for the socioeconomic factors and site. Although the interaction term is of primary focus, such a model will provide an overall appraisal of the association between health literacy and various covariates. On the basis of PI's previous work involving the ASL-NVS, one can alternatively characterize health literacy as a categorical variable with categories of adequate (NVS score of 5-6), indeterminate (2-4), and inadequate (0-1). As a secondary analysis, we will conduct an ordinal logistic regression with the categorical outcome of health literacy using the same covariates in the model as mentioned above.

Analyses for Aim 3

Building on the methodology used in previous Web-based search behavior studies [46], participants' search skills and success in addressing the clinical scenario tasks will be assessed using a combination of methods. First, based on the browser log and interaction data gathered by the usability software, we will compute summary statistics, such as the total time (in minutes) spent in searching, the number of unique websites and pages visited, and the number and characteristics of queries issued, involved in completing each task. Second, we will include time-based retrieval measures [47] that can characterize and quantify how a participant's search progress evolves over time. Knowledge acquisition will be measured by the number of correct responses based on the clinical vignettes (score range

between 0 and 12). All measures representing navigation skill and knowledge acquisition will be compared across levels of health literacy (adequate vs intermediate/inadequate) on the subgroup of the preselected 30 Deaf participants using 2 sample *t* tests. Although it is anticipated that power will be low to observe statistical significance, the primary objective for this comparison is to identify trends. Search progress for the clinical scenarios will be defined in terms of the quality of health information pages found during the search task. To assess the quality of health information pages, the research team will evaluate the Web pages/resources returned by participant searches or visited by the participant via browser navigation in terms of accuracy and coverage of the target facts in the reference set. Any differences will be discussed until a consensus is obtained.

Analysis of the Elicitation Interviews

For the iterative analysis of the qualitative data obtained with the elicitation interview process, we will follow multiple steps: (1) thoroughly read the transcribed data, (2) generate initial codes, (3) search for themes and patterns among the codes and across participants, (4) review themes, and (5) define and name themes. Initial data queries will focus on questions that emerge from aims 1 and 2 and navigability and knowledge acquisition patterns as measured in step 1. As we learn more through the iterative elicitation interview/analysis process, emerging themes and questions will be explored. Video-recording data of the one-on-one interviews will be transcribed into English by a bilingual transcriber [10]. Field notes will be taken after each encounter to describe the context, primary content, and emerging concepts. Participants' data in aim 3 will also be linked with the data collected in aims 1 and 2 that helped inform questions in the elicitation interviews. This will be done through the use of joint displays, a state-of-the-art integration procedure in mixed methods studies used for visually matching results by domains and themes from the quantitative and qualitative data to link the relevant information. All raw data video files will be uploaded onto a secure server, transcribed at the PI's office, and analyzed by the qualitative team. The use of Dedoose software [48] will allow transcription and detailed annotation to be tagged with video data of Deaf signers. All qualitative data (transcripts and field notes) will be coded independently by multiple investigators. Codes will be developed using consensus. A codebook will be created initially using navigation and knowledge acquisition and will be expanded with emergent codes. All transcripts will be coded by the research team (shown above) using the codebook in Dedoose.

Results

The project received human participants approval from the University of Michigan IRB (HUM00132918) to provide oversight to the 3 other research sites. Data collection will be completed in late 2020. Findings from this study will be used to advance what is known about health literacy and health information accessibility for the Deaf population. The findings will help explain how Deaf individuals access, navigate, and comprehend Web-based information. This study will help guide formulation of health information and health literacy interventions that more accurately take advantage of visual learning skills, even for those who have normal hearing. The findings will also be potentially beneficial for website editors. On the basis of the findings, recommendations for improving accessibility to health information for those who are non-English speaking and for those with inadequate health literacy will be provided. Results will be published in peer-reviewed journals once completed.

Discussion

Principal Findings

This project will advance knowledge on the origins of inadequate health literacy among Deaf individuals, including how effectively they access Web-based health information. In this paper, methods developed for the study will help assess the role of information marginalization on health literacy in the Deaf population. We also describe our approach to adapt instruments and measures applicable for Deaf ASL users. This project is the first to systematically explore health literacy for Deaf individuals. Most Deaf studies focus on Deaf health knowledge gaps and disparities, but our goal is to provide tangible recommendations going forward, especially for those involved with health information dissemination and website editors.

Direct Impact

Improvement in translation work and their processes can have an important impact as it affects other funded research projects and those that are being proposed. Furthermore, existing measures (eg, ASL-NVS) will be shared with other investigators interested in working with this population. We hope that the measures can be incorporated into community and clinical surveillance to help them manage their own health and determine how health information may or may not be reaching these individuals. Research with these communities are highly underfunded. This project provides an example of feasible research with the Deaf community. In addition, little is known about the predictors of health literacy in Deaf populations and how this affects their ability to use Web-based health information. This is key because of their social and information marginalization and their documented risk for inadequate health literacy. Web-based health information, if accessible, can provide a strategic approach to address the community's health knowledge gaps.

The results of this mixed methods proposal will significantly advance what is known about health literacy and health information accessibility for the Deaf population. This innovative study will generate rich data on how to formulate health information and health literacy interventions more accurately to take advantage of visual learning skills. The study results will be provided once data collection is complete (anticipated in 2020). Once finalized, findings will be used to develop a white paper on how to structure Web-based health information in a way that maximizes accessibility and comprehension for Deaf individuals and also includes strategies that adhere to universal health literacy precautions because of the Deaf population's documented risk of inadequate health literacy.

Timeline and Challenges

It is important to establish adequate time and resources to ensure adequate translation and adaptation of instruments needed in the project. This process took longer than anticipated. It also requires a diverse team to ensure good comprehension. We also needed to do 1 additional step and elicit feedback from the advisory board and the staff member at each site to make sure there were no issues (eg, regional variations for certain signs). It was decided that interviewer-administered questionnaires were preferred because of participant's different levels of language fluency. Although this did not yield a computerized self-administered tool, it was done to reduce any potential data collection errors or language/cultural discordance with Deaf participants. In addition to the TWG, our research team required extensive training to ensure strict protocol adherence, given the multiple study measures. In preparation for going into the field, we conducted both a site-specific workshop and an in-person workshop with all staff and investigators together to standardize interviews, administration of instruments, and data entry required for the study. Furthermore, to avoid participant fatigue with multiple measures, we plan to offer refreshments and ample opportunity for breaks during the data collection visits.

Conclusions

Research involving Deaf individuals requires careful consideration of instruments and measures that will not cause measurement bias, cultural discordance, and inaccessibility issues. Furthermore, dedicated time for adaptation, translation, and, if needed, validation steps should be factored when calculating the appropriate research time and funds needed to implement the project. Adequate training time is needed when conducting a multisite study involving several research staff. The results from this mixed methods proposal will advance what is known about health literacy and health information accessibility for the Deaf population. This study will also be useful to develop best practices in improving the accessibility and usefulness of Web-based health for individuals at risk for inadequate health literacy.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Random ordering of measures.
[DOCX File 19 KB - resprot_v8i10e14889_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the National Institutes of Health.
[PDF File (Adobe PDF File)233 KB - resprot_v8i10e14889_app2.pdf]

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Abbreviations

ASK: attitudes, skills, and knowledge
ASL: American Sign Language
ASL-NVS: American Sign Language-Newest Vital Sign
ASL-SRT: American Sign Language Sentence Reproduction Test
CAB: community advisory board
CTT: Color Trails Test
eHEALS: eHealth literacy Scale
eHealth: electronic health
HL: hearing level
HMC: Hurley Medical Center
IQ: intelligence quotient
IRB: institutional review board
KBIT2: Kauffman Brief Intelligence Test, Second Edition
NTID: National Technical Institute of the Deaf
NVS: Newest Vital Sign
PI: principal investigator

TOEL3: Speaking Grammar Subtest of the Test of Adolescent and Adult Language, Third Edition
TWG: translation work group

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Protocol

Visual Analytic Tools and Techniques in Population Health and Health Services Research: Protocol for a Scoping Review

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Abstract

Background: Visual analytics (VA) promotes the understanding of data using visual, interactive techniques and using analytic and visual engines. The analytic engine includes machine learning and other automated techniques, whereas common visual outputs include flow maps and spatiotemporal hotspots for studying service gaps and disease distribution. The principal objective of this scoping review is to examine the state of science on VA and the various tools, strategies, and frameworks used in population health and health services research (HSR).

Objective: The purpose of this scoping review is to develop an overarching global view of established techniques, frameworks, and methods of VA in population health and HSR. The main objectives are to explore, map, and synthesize the literature related to VA in its application to the two main focus areas of health care.

Methods: We will use established scoping review methods to meet the study objective. As the use of the term visual analytics is inconsistent, one of the major challenges was operationalizing the concepts for developing the search strategy, based on the three main concepts of population health, HSR, and VA. We included peer reviewed and grey literature sources from 2005 till March 2019 in the search. Independent teams of researchers will screen the titles, abstracts and full text articles, whereas an

independent researcher will arbiter conflicts. Data will be abstracted and presented using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist and explanation by two independent researchers.

Results: As of late August 2019, the scoping review is in the full-text screening stage. Data synthesis will follow and the first results are expected to be submitted for publication in December 2019. In this protocol, the methods for undertaking this scoping review are detailed. We present how we operationalized the varied concepts of population health, health services, and VA. The main results of the scoping review will synthesize peer reviewed and grey literature sources on the main methods of VA in the interrelated fields of population health and health services research from January 2005 till March 2019.

Conclusions: VA is being increasingly used and integrated with emerging technologies to support decision making using large data sets. This scoping review of the VA tools, strategies, and frameworks applied to population health and health services aims to increase awareness of this approach for uptake by decision makers working within and toward developing learning health systems globally.

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KEYWORDS

data mining; data visualization; population health; public health; health services research; machine learning

Introduction

In the first formal use of the term *visual analytics* (VA) in 2005, Thomas and Cook defined it as the "science of analytical reasoning facilitated by interactive visual interfaces" in their seminal book, Illuminating the Path [1,2]. VA techniques have proven helpful to professionals in gaining insights into the ever-expanding world of large complex datasets and unstructured big health care data [3,4].

Beyond Traditional Statistical Analysis

Although VA moves from traditional to exploratory data analysis, it brings together fields of data processing, management, mining, analysis, information visualization, and human-computer interaction [5-7]. It takes the power of traditional statistical analysis further by promoting an understanding of data with effective visual interfaces [1,8]. Typically, a VA tool uses a dimensional database model, as opposed to a relational database, whereas the analyst uses visual tools to develop interactive graphic displays that can further *drill* down to help explore and present summarized data [3]. These techniques offer an edge over traditional statistical analysis, which is limited because of humans being vulnerable to information overload [8,9]. VA tools offer a combination of *analytics* and the *interactive visualization* engines [10]. The analytics engine component involves data storage, transformation, and analysis, whereas the visualization engine provides functionality toward data manipulation and display [10].

VA techniques in health care also make use of machine learning for mining and automated analysis [4,11]. As a multidisciplinary field, VA is more than data or information visualization; its approach combines analysis, visualization, and human cognition [7,12]. This enables deeper insights for planning interventions through analytical reasoning, taking advantage of human cognition in processing visual representations and human-information interaction [10]. Interactivity is an important characteristic of VA interfaces, providing decision makers with the ability to explore data from multiple aspects and allowing for meaningful and enhanced visual representations that can be used toward evidence-informed decision making [13].

Visual Analytics in Health Care: Advantages and Applications

VA is an increasingly popular method for exploring, analyzing, and communicating results from complex big data in health [14]. Although it is increasingly applied in the clinical sciences, there is a lack of literature synthesizing VA methods, frameworks, and tools in population health and health services research (HSR) [15]. This is especially important with the rising demand from clinicians, administrators, patients, and policy makers for innovative means to answer complex questions [1,16]. Through this scoping review protocol, we present our methodology for the exploration of VA in the overlapping areas of population health and HSR to address this gap in the literature. The methodology presented will also be useful for future studies replicating similar concepts and for conducting reviews on related topics.

Given their high volume, variety, and velocity, much of public health data can be categorized as big data [10]. Ola and Sedig point to 4 major advantages of how VA can meet the needs of diverse users in public health, which can be extended to population health and HSR. These include overall flexibility to select the most suited visualization form, interaction control with data and information, nonlinear exploratory analysis, ability to provide tailored reports according to various audiences, and task adjustment for advanced and nonadvanced users alike [10].

One of the primary aims of population health and HSR is to better understand disease distribution and barriers to equitable care. Defined as "research with the goal of improving the efficiency and effectiveness of health professionals and the health care system [17]," HSR encompasses a large area of research. The concepts of HSR and population health are intertwined: first, in the purview of studying problems through an overarching population lens, and second, through a health systems lens. The *population health approach* brings together the two in their application toward health sector reform, allowing

researchers to formulate proposals for the organization and delivery of health care systems [18,19].

The efficiency and effectiveness of VA in data analysis and communicating issues in health care are being increasingly utilized [8]. VA techniques can be applied to complex and multiple data sources, including administrative databases, text-based electronic medical records (EMRs), and multiple data sources. The value addition of VA can be best illustrated by a few examples: Alberta Health Services' live dashboards on health service performance shows the service utilization by geography, type, and other variables [20]; population mobility from various sources for identifying pandemics through large interaction graphs and flow maps [15]; clustering of disease incidence and prevalence, broken down by seasonality and location [21]; detecting and promoting the understanding of spatiotemporal hotspots for emerging disease trends and associated factors using multisource complex spatiotemporal data [22]; complex gene-related data analysis to increase accuracy and avoid errors [23]; and exploring health events in geographic areas such as cities and towns to prevent hospital admissions [24].

Gap in the Literature

Despite the increasing and varied use of VA techniques, the term *visual analytics* lacks an accepted definition in the field of health care and can imply different ideas and applications. We found the use of the term for dashboards in critical care to disease surveillance using spatiotemporal techniques. Considering the fast growth of VA to answer complex health care research questions, clarification and categorization of the term and its application are needed.

Our preliminary literature search revealed various methods, frameworks, and use cases developed primarily by computer scientists working in the fields of advanced data mining, machine learning, and analytics. Shneiderman et al's seminal "overview first, zoom and filter, then details on demand" mantra lays down the most basic workflow tasks related to the type of data under study [25]. We similarly considered Chuang et al's [26] development of tools for textual analysis and Munzer's [27] 4-level nested model for the design and validation of visualization systems [28]. The field is fast developing, with multiple methods, frameworks, and tools that could have potential applications to health care data.

Recent reviews on VA in the clinical sciences show that the technique is being used for different conditions, specialties, populations, and levels of care [3,14,29]. In population health and HSR, VA techniques are being applied to complex questions, with varied applications ranging from hospital stay to decision support on pandemics [13,15,30]. While formulating our research objectives, we identified peer-reviewed and gray literature sources on VA methods, frameworks, and strategies in these fields, such as the use of multipanel graphs for epidemiologists [8], VA methods for studying electronic health records (EHRs) and anesthesiology [3], and spatiotemporal hotspots [22]. We also considered recent reviews related to VA. Wu et al's review presents the various methods and approaches for evaluation of health visualizations and VA while identifying the best practices [31]. Similarly, Islam et al's review summarizes data mining applications and theoretical perspectives in health care analytics [29].

Novelty of the Scoping Review and Protocol

As the number of health-related scoping reviews steadily rise each year, so does the need for protocols that address specific methodological challenges [32,33]. This protocol is of interest because the subject is substantially complex to scope because of the following reasons: (1) the multidisciplinary and intersectional nature of VA, (2) the broad areas and overlapping subject matter that *population health* and *health systems research* cover, (3) the nondiscriminatory nature of the terms in searching for literature in databases, and (4) the necessity of formulating research solutions methodologically to address these major challenges. In this protocol, we outline how we overcame these challenges to design an innovative review that was feasible, while encompassing an important subject area that has not been covered in a review so far.

This protocol outlines the scoping review methodology related to examining the state of the science of VA in the areas of population health and HSR. We first define the concepts, objectives, and research questions, followed by the design and methods. We discuss the expected results and contributions from the scoping review. In addition, we outline the challenges and solution we developed, allowing for feasibility, while maintaining rigor in a subject area not covered so far. We also present how we operationalized the search strategy for the 3 major concepts—population health, HSR, and VAs—that was undertaken over a course of 3 months, with the help of a multidisciplinary team and a dedicated information specialist. The search strategy was externally peer reviewed. The protocol is innovative and would prove helpful to researchers working in related areas and other stakeholders as the methods are replicable for other sectors. Through this protocol, we further aim at a higher level of transparency in reporting methods, maximizing rigor through peer review, and avoiding duplication of efforts.

The proposed scoping review is novel in summarizing VA methods that have been applied to cases in population health and HSR, using structured or unstructured, complex big data from single or multiple source(s). Furthermore, we focus on the application, frameworks, and methods that involve actual, proposed, modeled, or simulated data with end products that can be valuable to population health and HSR practitioners. We expect a small degree of overlap with reviews on health informatics and data mining, given that the technique has only been recently taken up in health care sciences [29,31]. However, to the best of our knowledge, there is no synthesis of literature on the use and application of VA as an important and quickly developing method in the interrelated fields of population health and HSR.

Objectives and Research Questions

The overall purpose of this scoping review is to develop an overarching global view of established techniques, frameworks, and methods of VA in population health and HSR, using any type of data. The main objectives are to explore, map, and synthesize the literature related to VA, including the use of the

term *VA* and its application in population health and HSR [34]. We will specifically examine the extent and nature of the literature on use cases of VA tools, techniques, strategies, and frameworks.

On the basis of Joanna Briggs tools for conducting systematic scoping reviews, we defined the major constructs of the review under population, concept, and context [32]. As this is a review on the methods of data analysis, we do not constrain the review to a population. The concept includes VA in population health and HSR, distinguishing it from conventional data visualization techniques, at different levels of analysis, including health service access and utilization.

Methods

Guidance Frameworks

To guide the scoping review methodology, we will primarily use the guidance established by Arksey and O'Malley [35], with improvements suggested by Levac et al [36] and Peters et al [32], with recent adjustments made by Tricco et al [37]. Methodological steps included identifying the research question; identifying relevant studies; study selection; charting the data; and collating, summarizing, and reporting the results [35]. The latter 2 groups' work helps with contextualizing these steps toward the specific review.

Study Outcomes and Eligibility Criteria

We identified the research questions following extensive consultations with the protocol authors to clarify the concept and purpose of the review. We considered the major question of studying VA in population health and HSR with the varied terminology used in the literature. Delineating VA from concepts such as information data visualization, which may or may not be *interactive*, is considered a major challenge for the review. We sought to limit this challenge through developing a detailed a priori eligibility criteria for the literature, with the types of literature to be included. The eligibility criteria are presented in Textboxes 1 and 2. The criteria are not considered exhaustive and will be developed further during the review.

As recommended by Levac et al [36], we considered the intended outcome of the review, which was to develop an overarching global view of established techniques, frameworks, and methods of VA in population health and HSR. It was also necessary to define this concept in relation to the search strategy to make the review feasible in terms of its time and scope. We will report the results based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist and explanation [37].

Textbox 1. Inclusion criteria for literature.

Inclusion criteria
1. Peer reviewed or conference papers.
2. Articles on population-level metrics: access, utilization, disease/condition distribution, and social/multiple determinants of health.
3. Articles that have interactive or exploratory techniques for spatial, temporal, spatiotemporal, and geospatial visualizations.
4. Articles on electronic medical and health records but with a clear population level or health services research component.
5. Articles with machine learning, natural language processing, automated analysis, data mining techniques, interactive tools, and iterative analysis.

Textbox 2. Exclusion criteria for literature.

Exclusion criteria
1. Editorials, projects, or reports.
2. Studies conducted in clinical settings.
3. Articles for individual condition(s) from a single hospital/unit, such as intensive care, surgery, and anesthesia without a population component.
4. Articles on device or sensor data without a population component.
5. Studies that include static data/information visualization/techniques, including simple bar graphs.
6. Studies that do not include an analytic component or do not use big data sources.

Identifying Relevant Literature

Operationalizing Concepts of Population Health and Health Services Research

One of the major challenges for this review was operationalizing the concepts for developing the search strategy. To aid with this, the scoping review team includes an information specialist (JB). The search strategy is based on 3 main concepts: population health, HSR, and VA. Population health has only recently been added as a Medical Subject Headings term in 2018 in MEDLINE [38], whereas *health services research* and *visual analytics* are nonspecific search terms. We detail the steps taken for operationalizing these concepts below.

We studied recent systematic and scoping reviews for the search strategies employed for operationalizing the population health, health services, and VA concepts. Table 1 describes the concepts, sources, and search terms extracted. For population and public health, experts have attempted to develop a common

language related to what both areas and terms encompass [39]. Alpi et al described the challenges in searching the literature because of the broad nature and often interchangeable and overlapping use of both terms [40]. Researchers take varied approaches toward strengthening their search strategies. In a review of the methods and application of EHRs to population health, search concepts ranged from infectious disease to social epidemiology [41]. Two reviews strengthened the searches using a broad search strategy and filtering studies based on objectives and eligibility criteria during the screening stages [42,43]. Searches were also complemented with citation and cross-reference methods for identifying the relevant literature [43].

For operationalizing the population health concept, we gathered related terms used by the national public health language created by the National Institute for Health and Care Excellence, UK version 1.2 [44]. We then identified the relevant search terms from detailed database trees. We also compared search terms from these sources and 5 recent reviews in population health [19,41,45-47], for example, Fone et al presented a detailed search strategy for population health [46], which we adapted for our use.

As for HSR, we searched recent reviews for operationalizing the concept in combination with the filters developed by the National Library of Medicine [48]. We identified and used 4 reviews [18,49-51] to translate the concept to the search strategy (Table 1).

Table 1. Operationalizing concepts and search terms from reviews on population health, health services research, and visual analytics.

Concepts and terms	Reviews mentioning the search strategy and terms
Population health; population health; public health; surveillance: sentinel, biosurveillance, and population health; spatial epidemiology; spatiotemporal; precision: public health, population health, and surveillance; population health outcomes	Etches (2006) [45]; Cohen (2004) [19]; Fone (2003) [46]; Singh (2014) [47]
Demographic; preventive health; population health	The National Institute for Health and Care Excellence (2007) [44]
Geographic information systems; environmental epidemiology; social epidemiology; health determinants	Casey et al (2016) [41]
Health services research; health services research; health care/data; equity and inequity; process; outcome; appropriateness; access to care; utilization/health care utilization/health service utilization; quality/quality improvement; cost; outcome disparities; system interventions; planning; geospatial; decision support; evaluation; monitoring; financing; health service delivery	Health services research filters developed by the US National Library of Medicine [44]; Canadian Institutes of Health Research (2018) [17]; Thompson et al (2016) [49]: no search strategy, uses CIHR 2018 definition; Gulley et al (2018) [50]; Rowland et al (2014) [51]; Harris et al (2012) [18]
Visual analytics; visual analy* ; data visualization; interactive; automated analysis; dashboard; information visualization; data exploration; interactive data exploration; mathematical simulation/modeling with visualization/dashboard; big data analytics; predictive analytics; descriptive analytics; prescriptive analytics; big data	Reviews: Islam et al (2018) [29]; West et al (2014) [52]; Simpao et al (2014) [3]; Wu et al (2019) [31] and seminal articles: Basole et al (2015) [53]; Basole et al (2015) [54]; Caban and Gotz (2015) [16]; Falster et al (2014) [24]; Hosseinpoor et al (2018) [55]; Huang et al (2015) [56]; Martinez et al (2016) [57]; Ratwani and Fong (2015) [58]; Simpao et al (2015) [14]

Operationalizing Visual Analytics

VA is a specific term denoting specific approaches and techniques [1]. However, the term is vague, and alternate terms such as *data and information visualization* are used in the literature. We identified and used 4 major recent reviews related to the subject [3,29,31,52], along with 9 seminal papers [14,16,24,53-58], to identify the search terms (Table 1).

Defining Interactivity in Visual Analytics

Interactivity is usually stated to be one of the recent hallmarks of VA applications, owing to the manipulation of visual interfaces afforded by computing power [10]. We borrow from Ola and Sedig's and Pike et al's work to define *interactivity* as the ability to reflect changes in the visual representation of data based on one or more indicators available on the analytic interface to the user [10,59]. Pike et al categorized interaction elements into 2 main types: (1) *lower level* aimed at change of the visual representation to study patterns, relationships, and (2) *higher level* offers understanding of the intent of interaction itself toward knowledge discovery [59]. For selecting appropriate literature as part of this scoping review, we mainly focus on the *lower level* interaction that would allow tasks such as filtering; determining ranges; and finding anomalies, clusters, and the like by providing menus, dropdowns, and other options on the visualization interface. We expect to increase the accuracy for selecting VA literature, while having minimal overlap with other noninteractive visualizations that typically would not fall under VA. In addition, we will focus on VA literature that uses advanced techniques within the analytic engine, such as machine learning and natural language processing.

Final List of Search Terms

For developing the final list of search terms, the process for each concept was not necessarily linear. We constantly compared the list of terms from each step within each concept with detailed database trees to check that we included relevant concept components, while avoiding duplication of results. Following this methodology, we were able to control the *noise*

in constructing the search strategy, making it manageable and feasible.

Search Strategy: Peer-Reviewed Sources

We have limited this review to formal VA methods, applications, and tools that have been either published as peer-reviewed literature or as full conference papers. Using the 3 main operationalized search concepts, the information specialist (JB) developed a search strategy in MEDLINE (Multimedia Appendix 1). We validated the search strategy by ensuring that it captured the key seminal studies about VA in population health and health care, in general, to ensure that the subject literature was included as broadly as possible. We limited the search to English language articles from 2005 onward to coincide with the formal use of the term *visual analytics* by Thomas and Cook in their seminal book, Illuminating the Path, in 2005 [1,2].

For fine-tuning and improving the search strategy for peer-reviewed articles in health-related databases, the strategy was peer reviewed by another information specialist at the University of Calgary, using the latest Peer Review of Electronic Search Strategies: 2015 Guideline Statement [60]. After incorporating the suggested revisions, the MEDLINE search yielded 4563 articles and included all 12 seminal studies. The MEDLINE search strategy will be adapted to EMBASE and other databases. Databases that are not primarily health related, such as from geography, mathematics, computer science, or engineering disciplines, will not be searched.

Capturing Gray Literature and Complementary Searching

During our initial searches, we realized that VA methods and representations such as dashboards are presented at conferences in real time, whereas the proceedings include full papers. Given VA's fast development, this was considered a rich resource that differs from peer-reviewed literature.

We will capture the gray literature through translating the MEDLINE search to Web of Science, Compendex, and Inspect to identify full conference papers. Conference abstracts were excluded from the search for reasons of clarity and completeness of information. An abbreviated search will also be conducted in IEEE Xplore, a subject-specific database. In addition, we will complement our strategy with the searching of reference lists within peer-reviewed and gray literature sources and hand searching subject-specific journals and conference proceedings. These include *Applied Clinical Informatics*, *Visual Analytics in Healthcare*, *IEEE Transactions on Information Technology in Biomedicine*, *Journal of Medical Internet Research*, *Journal of Medical Systems*, *Journal of the American Medical Informatics Association*, *Health Affairs*, *Journal of Biomedical Informatics*, *Healthcare Informatics Research*, and *PLoS ONE*. Both the IEEE Xplore search and the list of journals are based on Islam et al's review on data mining in health care [29] and a Web search by the authors. A Google Scholar and Google Web search engine review will also be conducted, limited to the first 100 results on both platforms.

We will not include dissertations, theses, and book chapters in the review. Furthermore, we will not search for data visualization websites, as it was deemed impossible to gather this huge body of data, adjudicate on the methods and results, and synthesize findings. In addition, frequent content and hyperlink changes would render these sources unusable to future readers in a short time. All citations retrieved will be amalgamated and managed using Clarivate Analytic's Endnote citation management software [61].

Study Selection

A priori selection criteria have been developed, which will be modified during the study selection process, as required. Following the methodology suggested by Levac et al, 2 reviewers will independently review the titles and abstracts to categorize whether the piece of literature is eligible for full review [36]. We expect at least 8000 articles, each of which will be randomly assigned to 2 reviewers. Studies that do not fall in either category or represent conflicts between the reviewers will be resolved by an independent referee. We will retrieve full-text results for the included studies and any unresolved studies for inclusion. In addition, 2 reviewers will screen the full-text results independently for inclusion in the next stage of the review. An expert third party will adjudicate in case of unresolved decisions for inclusion of studies at any stage. We will use the DistillerSR Web platform for efficiently managing the title and abstract review, full-text screening, and abstraction of data [62].

We will include published and in-press peer-reviewed articles, conference papers, and relevant gray literature sources that include quantitative, qualitative, and mixed method studies, tools, frameworks, and methods of the use of VA. All studies that mention *VA* as a method in population health and HSR, and at any level of both of the latter concepts, will be included, for example, VA methods for assessing an emergency room population over time will be included. Single disease visualizations at any facility or geographic level will not be included in the scoping review if these are meant to be used toward clinical decision making. However, any studies dealing with population metrics and health services indicators will be included. Furthermore, we will not include methods that may have an application to health care but were not applied to an actual or hypothetical health care research data. This is important as we limit ourselves to the application of VA to health care. We also include studies on EMR/EHR data if the research question or application is in population health or health services.

VA applications also borrow from and overlap with machine learning and natural language processing and can involve complex datasets, unstructured text data such as from EMR sources, and linked analysis. We will include and focus on articles that include any type of mining, querying, and analysis technique that includes VA application to HSR and population health. However, we will not include articles related to data preparation/harmonization, user experience and preference, and human-information and human-computer interaction. The eligibility criteria are given in Textboxes 1 and 2.

Data Extraction

A data abstraction form will be developed and pilot tested by 2 teams composed of 2 researchers each, all working

independently of each other. The data form will be tested on 5 to 7 articles for consistency and comprehensiveness for capturing relevant data. Changes will be made in a team meeting to discuss and compare the pilot test results. On the basis of the studies used for developing the search strategy, the proposed fields for abstraction include author last name, year, full journal name, reviewer's initials, study type, article type, setting, geographic location (country and continent), and tools and method type (temporal and spatiotemporal). We will try to draw a distinction in the use of methods within the visual and analytic engines, if possible, especially related to machine learning, natural language processing, and other automated methods. In this regard, we have opted not to use the term *artificial intelligence* as it is nonspecific. Furthermore, the abstraction fields will include innovation and impact of the VA method/uptake of the method, target user/audiences, settings for the use of the VA solution, and potential application toward knowledge translation. Two reviewers will review and chart the data independently for each article.

Results' Synthesis and Presentation

Abstracted information from all the included articles will be synthesized, and the results will be presented to capture the extent of the literature. First, tables will provide the basic information on the types of studies included, the use of VA in various areas of population health or HSR, and the major tools and frameworks used. This overview will be followed by a narrative presentation of the synthesized mapping of the included literature. The tables and presentation will be developed considering the abstracted results. We are not limiting the review to being reported against a said framework at this point; however, we intend to use the guidance provided in Levy and Ellis's paper on reporting reviews on information systems [63], which was selected on the basis of its subject-specific reporting. The authors cite the potential problems in reporting findings in such reviews, suggesting to place them in the wider context of the body of knowledge and the research itself, while building on a theoretical foundation [63].

Results

As of late August 2019, the scoping review is in the full-text screening stage. Data synthesis will follow and the first results are expected to be submitted for publication in December 2019.

Discussion

Comparison With Prior Work

Recent scoping and systematic reviews on the related subjects of analytics and data mining show that VA is being increasingly taken up as a method of choice for big data in health care [1,6,19]. In population health and HSR, VA techniques are being applied to complex questions of service delivery and disease distribution [2,15,20]. Recent reviews include methods and approaches for evaluation of health visualizations and VA [24] as well as data mining applications and theoretical perspectives in health care analytics [22]. The proposed scoping review is novel in summarizing VA methods that have been either applied or proposed to use cases in population health and HSR, using structured or unstructured, complex big data from any or multiple source(s). To the best of our knowledge, there is no synthesis of literature in this area, which will add to the body of literature on these evolving methods of analysis toward complex health care data.

Limitations

This scoping review methodology does not include book chapters, theses, short papers, editorials, nonpeer-reviewed reports, conference abstracts, and live websites using VA techniques for reasons mentioned above. We also limit the use of VA methods from 2005 onward that have been applied to population health and HSR. Finally, we do not explore subject-specific databases, such as from geography and computer science, which may limit our findings to proposed or established methods that have been either published or presented. However, we focus on casting a wide net to capture relevant methods for use cases in both population health and HSR. We devised the methodology in consultation involving a substantial number of multidisciplinary experts to advise on the rigor and feasibility of the review. We also hope to present the findings in 1 or more articles to illustrate the state of science for this important and emerging method.

Conclusions

This scoping review will attempt to provide a foundational understanding of the current landscape of VA within population health and HSR. VA holds tremendous potential for contributing to the learning health systems approach, allowing complex data analysis, and visualization toward improving practices. Mapping the existing VA tools, strategies, and frameworks to health data will promote the use of these methods, which are being increasingly taken up for embedded research and future initiatives in health services. This scoping review protocol describes the design for the review on VA methods in population health and HSR, and it also lays out methodological challenges and steps taken toward ensuring rigor. The latter can be applied and developed by researchers beyond the subject area.

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Authors' Contributions

All authors contributed to the manuscript writing, revision, and the search strategy. JB formulated and modified the search strategy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Medical Literature Analysis and Retrieval System Online search strategy.
[PDF File (Adobe PDF File), 256 KB - resprot_v8i10e14019_app1.pdf]

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Abbreviations

EHR: electronic health record
EMR: electronic medical record
HSR: health services research
VA: visual analytics

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Protocol

American Cohort to Study HIV Acquisition Among Transgender Women in High-Risk Areas (The LITE Study): Protocol for a Multisite Prospective Cohort Study in the Eastern and Southern United States

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Abstract

Background: In the United States, transgender women (TW) are disproportionately burdened by HIV infection. Cohort studies are needed to evaluate factors driving HIV acquisition among TW over time. These will require implementation strategies that are acceptable to the TW community and feasible to implement.

Objective: This study aims to investigate the rate and correlates of HIV acquisition and other health outcomes among TW in eastern and southern United States.

Methods: LITE is a multisite prospective cohort in 6 eastern and southern US cities, which will be followed across 24 months of technology-enhanced biobehavioral follow-up. Adult TW, regardless of HIV status, are recruited via convenience sampling (eg, peer referrals, social media, and dating apps). Participants are enrolled in a baseline study visit, complete a sociobehavioral survey, and test for HIV and sexually transmitted infections. Participants who are not living with HIV at baseline are offered enrollment into the cohort (N=1100); follow-up assessments occur quarterly.

Results: Cohort assembly was informed by synchronous Web-based focus group discussions with TW (n=41) and by continuing engagement with community advisory board members from each site. Enrollment launched in March 2018. The study is underway in the Atlanta; Baltimore; Boston; Miami; New York City; and Washington, DC, metro areas. As of March 2019, 795 TW

completed a baseline visit (mean age 35 years). The majority of the participants are racial/ethnic minorities, with 45% of the TW identifying as black and 28% of the TW identifying as Hispanic/Latinx. More than one-quarter (28%) of the TW are living with HIV infection (laboratory-confirmed). Online recruitment methods support engagement with TW, although peer referral and referral through trusted health facilities and organizations remain most effective.

Conclusions: This study is responsive to increasing research interest in technology-enhanced methods for cohort research, particularly for hard-to-reach populations. Importantly, the diversity of literacy, technology use, and overall socioeconomic situations in this sample of TW highlights the need to leverage technology to permit a flexible, adaptive methodology that enhances engagement of potential participants living in marginalized contexts while still ensuring rigorous and sound study design.

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KEYWORDS

HIV; transgender persons; United States; cohort studies; HIV infection

Introduction

Background

Transgender women (TW) are one of the populations most affected by the HIV epidemic in the United States and internationally. A recent systematic review of global health burden in transgender populations further situates the HIV epidemic alongside other health conditions disproportionately facing TW [1]. Multiple biological, behavioral, and social risks for HIV infection among TW are driven by, and/or concomitant with, structural barriers that limit access to HIV prevention, testing, care, and health services [2]. In Baltimore; Washington, DC; Boston; New York City; Atlanta; Miami; and other US metropolitan areas, TW report histories of sexual assault and violence, homelessness, unemployment, substance use, and low health insurance coverage [3-12]. Substantial barriers have resulted in low access to HIV prevention, care, and other health services for TW [13-15]. Owing to these contextual vulnerabilities, as well as the acquisition risks of anal sex, which are common among TW, TW bear a higher and more disproportionate burden of HIV than the cisgender, heterosexual population. These factors increase the risk for HIV acquisition, resulting in an estimated 14.2% (95% CI 8.7%-22.2%) laboratory-confirmed HIV prevalence (meta-analysis) overall and as high as 44.2% and 25.8% weighted prevalence among black and Hispanic TW, respectively [16].

Disparities in HIV prevalence exist across races and ethnicity [5,17,18], with HIV prevalence among black TW being approximately twice that of other TW [19]. Self-reported HIV prevalence among young TW (aged 15-24 years) has ranged from 19% to 22%, highlighting early risk and onset of infection [8,20]. However, HIV prevalence by self-report may be an underestimate, given the low rates of HIV testing among TW [21]. Community-based HIV testing among transgender populations in New York City, Miami, and San Francisco (n=559) demonstrated a high (12%) prevalence of newly diagnosed HIV infection among TW participants [21]. Risk factors for new infections and unknown HIV infection included having a partner with unknown HIV status in the past year and having been tested more than 12 months ago [21]. Gender-based discrimination and prioritization of gender affirmation–related health care serve as barriers not only to HIV testing but also to engagement in HIV care and treatment [22-24]. Limited international cohorts that include small samples of TW from the United States suggest high HIV incidence, ranging from 2 to 4 cases per 100 person years (pys), among TW and an urgent need to develop and implement HIV prevention interventions that are both effective and acceptable to the TW population [25-27].

Promising empowerment-based and counseling interventions have demonstrated reductions in HIV risk behaviors among TW and their partners [28,29]. However, pre-exposure prophylaxis (PrEP) interventions, which have proven efficacious for other populations, have not shown efficacy for preventing HIV acquisition among TW, and benefits for this population remain unclear [25,30-32]. Many epidemiologic questions remain for TW, including the following: HIV incidence and risk parameters to inform HIV prevention trials; efficient and appropriate methods for recruitment and retention of participants; identification and characterization of HIV microepidemics; methods for secure dynamic data and real-time data capture among participants, given challenges with technology; and robust estimates of HIV care after seroconversion. Although TW have contributed to international and domestic HIV epidemiology and prevention research, they have not been adequately represented to produce scientific inferences for the population of TW alone.

Several challenges have affected the study of HIV among TW in the United States. First, the lack of transspecific marketing, misgendering during research (referring to TW participant with incorrect names/pronouns), and inclusion of TW among other key populations, such as men who have sex with men, have left a legacy of wariness and hesitation among TW as it relates to participation in HIV research. Despite historical participation in HIV research, TW participants have reported feeling that the successes of these efforts did not result in benefits for the transgender community and that HIV research was often neither specific nor acceptable to TW. Moreover, TW participants have expressed a need for research on other health priorities [33]. These findings highlight the need to assess other health issues within the context of HIV research, recognize and respond to TW priorities, and carefully market and promote HIV research with input from and dissemination to the community. Finally, although technology-based methods (typically necessitating mobile phones and internet access) have emerged as more efficient and cost-saving approaches to recruitment and data

collection for HIV research, data have shown that TW frequently use social media, dating apps, and other internet-based media [34]. Our own experiences have found that mobile phone use is inconsistent among some TW because of loss/replacement of phones and temporary data plans. This suggests that thoughtful approaches to technology-enhanced methods for prospective study of TW are needed to ensure representation in research.

Objectives

The objective of the American Cohort to Study HIV Acquisition among TW in High-Risk Areas—known locally and by participants as *Leading Innovation for TW's Health and Empowerment* (*LITE*)—cohort study is to fill these critical scientific knowledge gaps in HIV prevention and care research and to translate findings into actionable interventions for TW in the United States. This study proposes to establish a multisite, racially/ethnically and culturally diverse prospective cohort of TW in eastern and southern United States to characterize HIV acquisition, risk factors for HIV infection, access to biobehavioral HIV prevention methods, and linkage to care for those who HIV seroconvert for the purposes of informing evidence-based and optimal HIV prevention interventions for this at-risk population. The specific aims of the study were as follows: (Aim 1) to determine the efficiency and acceptability of novel, technology-infused recruitment methods to enroll TW who are not living with HIV (here forward into a prospective cohort); (Aim 2) to describe the demographic, socioeconomic, behavioral, and physical and mental health profiles of HIV-uninfected TW in the first multisite longitudinal cohort of TW in eastern and southern United States; (Aim 3) to estimate HIV incidence, trends in incidence, and associated individual, social, and structural risk factors among TW in eastern and southern United States; and (Aim 4) to estimate the HIV Prevention Continuum (HIVPC) among HIV-uninfected participants and the HIV Care Continuum (HIVCC) among newly HIV-infected TW. The cohort will be supported by technology-enhanced recruitment and retention methods. This study will provide information needed about TW across 6 high-risk metropolitan areas (Boston; New York City; Baltimore City; Washington, DC; Atlanta; and Miami) in a region of the country where less is known about rates and unique risk factors for HIV acquisition among TW.

Methods

Overview

This is a multiple principal investigator (PI) study led by faculty from Johns Hopkins University (JHU; PI: Wirtz) and Boston Children's Hospital (BCH), Harvard University (PI: Reisner). The study is supported by leading research institutions, spanning eastern and southern United States, including the following: JHU, Baltimore, Maryland; BCH, Harvard University, and The Fenway Institute at Fenway Health, Boston, Massachusetts; Callen-Lorde, New York City, New York; Emory University and Grady Memorial Hospital, Atlanta, Georgia; University of Miami, Miami, Florida; and Whitman-Walker Health, Washington, DC. The coinvestigators in this team specialize in HIV epidemiology among key populations, transgender health and clinical care, sociobehavioral sciences, management and analysis of longitudinal cohorts, and cross-sectional incidence estimation and laboratory methods. All partner organizations are affiliated with or are themselves clinical sites serving TW, and they have established strong relationships with local community-based organizations that specifically offer services for TW. These relationships continue to be nurtured to ensure the study is acceptable to the transgender community and is consistent with TW's preferences in terms of study content, as well as to obtain valuable feedback on the study, which can support both recruitment and retention of study participants.

A virtual community advisory board (CAB) has been formed to facilitate research by serving as a mechanism for community consultation, and it will be engaged through every phase of the research activities. The CAB serves as a working partner and provides guidance to the research activities and consent processes; discusses concerns and protection of the community; and publicizes research activities, ancillary services, and results to the wider TW community [35,36]. The CAB is also comprised of transgender community leaders and those serving in transgender health care; it is representative of the diverse transgender communities residing in the high-risk locales enrolling this study, and it collaborates with investigators to foster meaningful research so that implementation is "with," not "on," TW [37]. The CAB took ownership by naming this project the LITE study.

Conceptual Framework

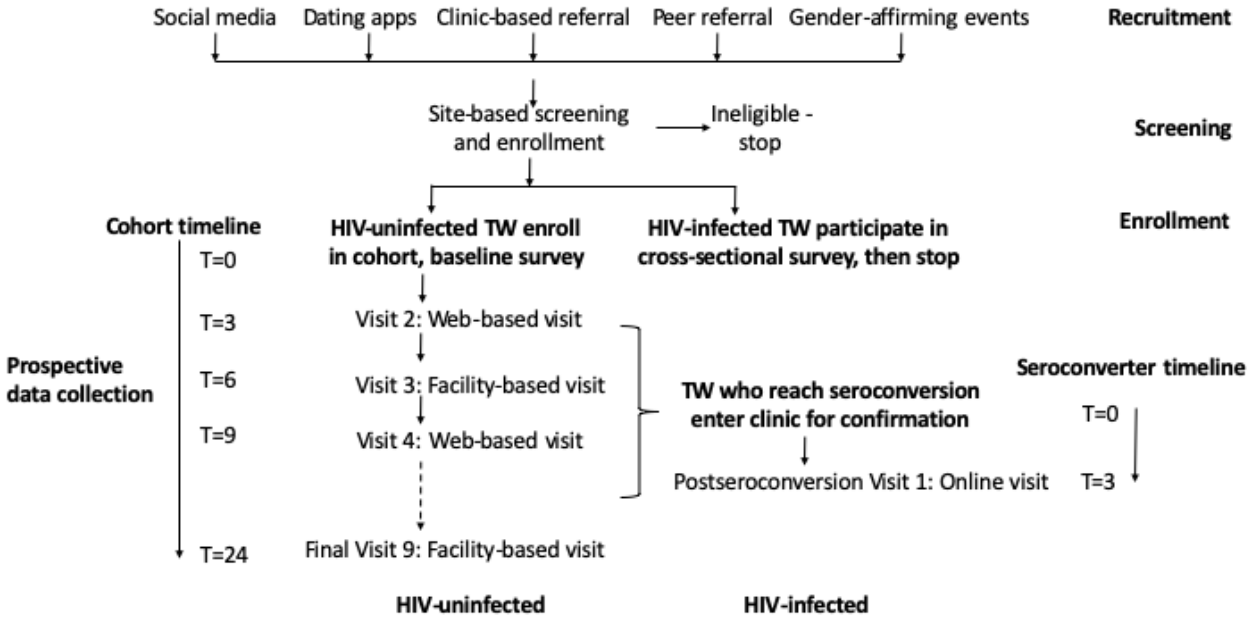
This study draws on the *situated vulnerabilities* conceptual framework, which conceptualizes HIV infection risk and acquisition among TW, as recently described by Reisner et al [1]. Several conceptual models have been applied to transgender health (eg, social determinants and social ecological models [38,39], gender affirmation [40], gender minority stress [41,42], syndemic production [43,44], and health and human rights approaches) [45,46]. These models overlap in their shared recognition that multiple and intersecting levels of risk (biological, individual, interpersonal, and structural) shape the distribution of diseases in transgender populations. Thus, we conceptualized the multilevel factors that fuel HIV risk and acquisition among TW as "situated vulnerabilities" [23,47]. The vulnerabilities that TW face regarding HIV acquisition are both sex linked (biological per-act probability of HIV transmission in receptive anal sex) and gender linked (socially derived exposures such as stigma, survival sex, and gender affirmation). We focus on identifying the "situated vulnerabilities" driving HIV acquisition in the TW cohort. At the biological level, TW with anatomically male partners face a high HIV transmission probability via condomless anal sex with serodiscordant and viremic partners [48,49]. Coinfection with perigenital or perianal sexually transmitted infections (STIs) may also potentiate the acquisition and transmission of HIV [50,51]. Network-level risks include a high prevalence of HIV and limited awareness of HIV status within transgender-inclusive sexual networks [52-54]. Community-level stigma and structural-level discriminatory laws also contribute to the high burden of HIV by limiting the provision and uptake of services as well as by driving TW to engage in sex work for economic survival and gender affirmation [23,40,55].

Design

This study focuses on the recruitment and development of an HIV-uninfected cohort as well as a cross-sectional HIV-infected comparison group. (Note: we recognize and prefer to refer to this group as "TW who are not living with HIV" to minimize stigmatization; however, for the purposes of this technical report, we utilize the term "HIV-uninfected" to refer to the diagnosis associated with study screening criteria.) TW, regardless of HIV status, are recruited via technology-based and nontechnology-based recruitment methods (Figure 1). HIV-uninfected TW who meet eligibility criteria are enrolled in the longitudinal cohort. TW who are recruited but are ineligible for the cohort on the basis of HIV infection are enrolled in a comparison cross-sectional sample and complete the same baseline survey and laboratory testing as the HIV-uninfected cohort.

HIV-uninfected TW are followed for a minimum of 24 months to estimate HIV incidence, trends, and risk factors for HIV acquisition (Figure 1). Following the facility-based enrollment visit, survey and laboratory data will be collected from cohort participants every 3 months using Web-based and facility-based visits. Web-based data collection utilizes an app-based self-administered survey and home HIV self-testing with photo validation of results. Any participant who seroconverts during the longitudinal study completes facility-based confirmation of HIV infection and is referred to affirming services for HIV care. Participants who seroconvert are followed for 1 additional study visit for the purposes of assessing prospective engagement in the HIVCC.

Figure 1. Study flow diagram. TW: transgender women.



Sample

The overall study sample, inclusive of formative research, baseline, and cohort participants, is comprised of TW adults, aged ≥18 years, assigned male sex at birth but identifying as women or along the transfeminine spectrum. Gender identity is verified during enrollment by using the recommended 2-step method, which measures sex assigned at birth (step 1) and current gender identity (step 2) [56,57]. Enrollment in the cohort is restricted to HIV-uninfected TW, which is laboratory-confirmed at enrollment.

Cohort enrollment eligibility is determined during the baseline study visit. Eligibility includes a negative baseline HIV test result and at least one of the following risk factors for HIV acquisition (as HIV incidence is the primary outcome of this study): (1) aged 18 to 24 years; (2) screens positive for alcohol use disorder; (3) reports engaging in condomless anal and/or vaginal sex in the previous 12 months; (4) reports lifetime history of sex work; (5) reports unstable housing in the previous 12 months; (6) reports sharing needles to inject hormones, silicone, and/or drugs; (7) screens positive for drug use disorder; (8) reports a lifetime history of injection drug use; (9) reports a lifetime history of incarceration; (10) reports STI diagnosis in previous 3 months; (11) has a positive STI diagnosis at baseline; or (12) reports current or recent (last 12 months) PrEP use. Participants currently enrolled in an HIV prevention clinical trial are excluded.

Generalizability of study results is optimized using multiple study sites across eastern and southern United States. All 6 metropolitan areas are diverse racially, ethnically, and culturally; it is anticipated that the final study sample will be equally diverse, given the team's past and ongoing research experience and the composition of TW served in clinical care services across sites. Findings may be less generalizable to rural areas; however, there is little known about the number of TW living in rural areas, and the use of online recruitment methods may facilitate participation of those living in more suburban and rural areas surrounding select metropolitan sites. Finally, the minimal use of facility-based data collection efforts during follow-up may help to protect against the Hawthorne effect that may compromise generalizability [58].

Formative Research

Formative, qualitative research was conducted between August 2017 and January 2018 with members of the TW population to inform recruitment, marketing, and app development. Qualitative research utilized computer-mediated communication (CMC; "Web-based focus groups") with focus groups comprising participants from across all 6 sites [59]. CMC provides multiple benefits in terms of reducing cost and barriers associated with finding an ideal time and physical space for participants to meet. Previous research comparing in-person with CMC focus groups has found that greater sharing of ideas occurs via CMC because of visual anonymity and that perceived distance of the internet stimulates group discussion and disclosure [60]. Our team has successfully used CMC with transgender participants previously [61].

Focus groups comprised 5 to 10 TW participants who met via video/teleconference at a mutually agreed upon time. Focus group participants were recruited using the same methods utilized to accrue the cohort and cross-sectional samples (see the Recruitment section), and maximum variation sampling was utilized to enroll participants across a wide range of race, ethnicity, age, geographic residence, and gender transition. Candidate participants were screened for eligibility (see the Sample section), regardless of HIV status, before enrollment, and they had the option to join by audio only, to use video, or to upload a photograph, depending on participant comfort and preference. Discussions were led by a facilitator, utilized audio communication to avoid delays associated with typed CMC, and followed best practices set forth for CMC qualitative research [60,62]. A professional Web-based meeting provider was used to maximize security, provide audio recording, and offer telephone options for participants without internet access. Semistructured discussion guides were used during data collection to identify preferred recruitment methods, assess acceptability of fingerprint or other verification methods for study participation, obtain input/feedback on study branding and app design, and identify concerns related to study activities.

Qualitative research was led by investigators from JHU and BCH (Wirtz and Reisner) using standardized methods for qualitative research with key populations [63,64]. Research was iterative in nature, bringing in results and new questions raised from earlier focus groups. An iterative, analytic approach followed Crabtree and Miller's 5-step approach to qualitative interpretation: (1) describing, (2) organizing, (3) connecting, (4) corroborating, and (5) representing [65]. Regular debriefing meetings were held with focus group facilitators to identify preliminary findings and facilitate iterative data collection and analysis. An initial set of codes were developed based on the core domains described above. Qualitative codes were then applied to transcripts and discussion notes using NVivo qualitative analysis software (QSR International) by 2 independent analysts. New codes were developed as they emerged. Summaries were developed for major themes and distinctions across subgroups. Corroboration included discussing preliminary findings and implications for the cohort study with the CAB. Preliminary findings informed subsequent cohort methods, and final analytic findings have been submitted for publication [66].

Recruitment

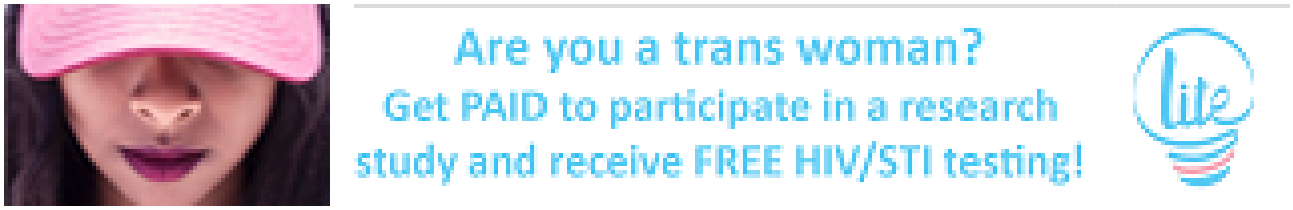
Study recruitment utilizes a mixed format of technology- and nontechnology-infused recruitment methods. Technology-infused recruitment methods include the use of geosocial networking (GSN) apps frequented by TW, such as Grindr, Black Gay Chat, and Tinder, as well as social media, including Facebook and Reddit, all of which have been successfully used to recruit other populations [34,67-69]. Figure 2 displays a banner advertisement that was developed for the dating apps. GSN and social media recruitment are geotargeted to the 6 metropolitan areas and surrounding regions [68]. Study banners, messages, and broadcasts use images of TW, which reflected the racial, ethnic, and gender presentation diversity; provide a study phone number; and link to the Web page in English and Spanish. GSN sites also collect statistics such as the number of impressions, clicks, and time of each click that are used for analysis of recruitment efficiency.

Nontechnology-based recruitment methods include peer referrals and clinic-based referrals (excluding HIV-related services) as well as venue-based recruitment from gender-affirming community events. We used nontechnology-based methods in addition to technology-infused methods, given past research that showed that despite Web-based outreach, only 21% of transgender participants learned of the study via the internet, with the remainder recruited by a peer or support group [70]. Peer referrals follow a modified respondent-driven sampling (RDS) technique [71], allowing enrolled participants to recruit other TW peers to the study by using uniquely numbered electronic short message service (SMS)–based coupons for recruitment tracking purposes. Gender-affirming community events focus on conferences that introduce the community to a range of health professionals serving the transgender community (eg, endocrinology, surgical), offer networking and social support, as well as offer legal clinics and other referrals.

Conferences include but are not limited to the following: First Event, Boston [72]; Philadelphia Trans Health Conference, which is frequently accessed by community members from Baltimore-Washington, New York, Boston [73]; the Atlanta's Transgender Health and Education Alliance's Peach State Conference [74]; and Southern Comfort, Fort Lauderdale [75], accessed by TW in the Miami area. Partnerships with these events for recruitment allow the research team to acknowledge TW's health and livelihood priorities and provide an opportunity to meet TW in a space that is gender affirming.

Participants are directed from study fliers, SMS text messages, or Web-based advertisements to the study Web page [76] where participants can complete an interest survey to be contacted by study staff or can directly identify the telephone number associated with their city and call to schedule an appointment. Candidates are required to attend a facility-based visit at the nearest study site for screening to verify eligibility (identify as TW based on a 2-step procedure [56,57], aged ≥18 years, and residing in/around 1 of the 6 metropolitan areas or surrounding regions) and complete baseline data collection. A unique identifier is created for participants to allow for secure access to follow-up surveys through the mobile app.

Figure 2. Electronic study flier.



Facility-Based and Electronic Study Visits

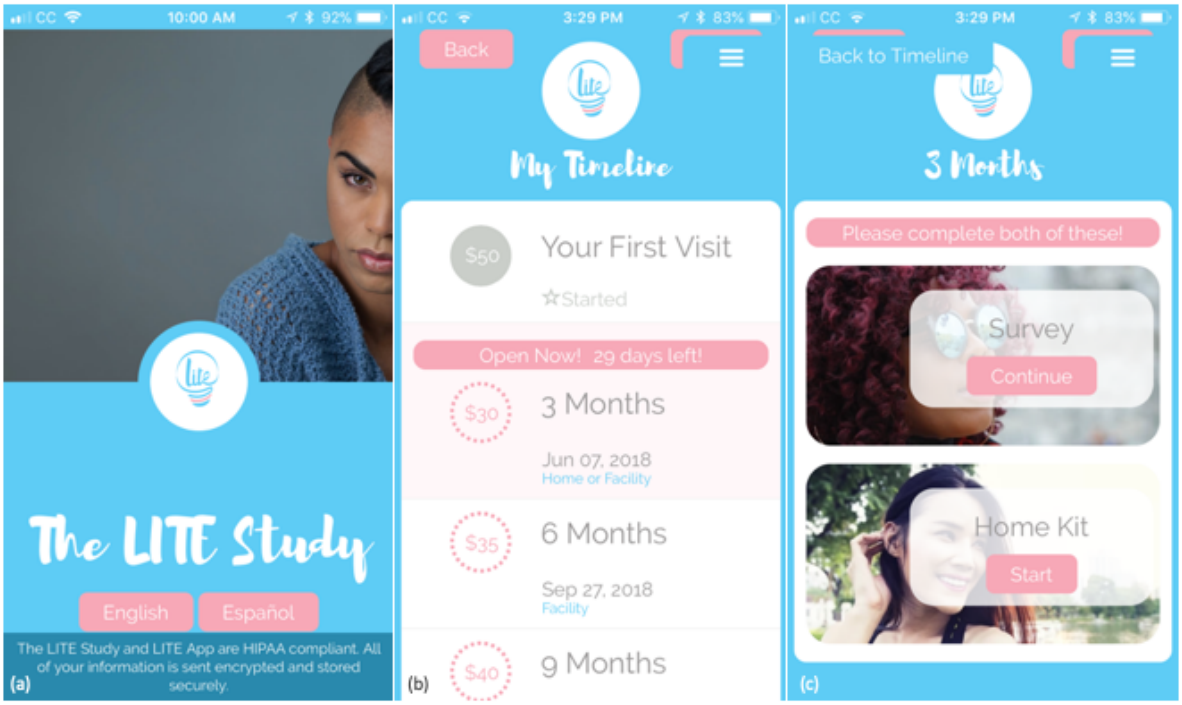
All TW who are recruited via the above-mentioned methods and meet eligibility criteria, regardless of HIV status, are asked to participate in a baseline survey, HIV and STI testing, and biospecimen collection. HIV-uninfected TW who meet cohort eligibility criteria are enrolled in the prospective cohort. TW who are recruited but are ineligible for the cohort on the basis of HIV infection are enrolled in a comparison cross-sectional sample and complete the same baseline survey and laboratory testing as the HIV-uninfected cohort.

Each cohort participant is followed for a minimum of 24 months (the duration anticipated for the funding duration, pending grant renewal). Survey and HIV self-testing results are collected from cohort participants every 3 months using a multimodal approach in which facility-based participation is required for baseline visit and 6-, 12-, and 24-month visits, whereas the rest are optional Web-based or facility-based visits (Figure 1). The required facility-based visits provide an opportunity to continue to build relationships between staff and participants, collect biologic specimens and test for STIs, and provide participants with additional HIV self-test kits that can be used at home in subsequent visits. Participants have the option to engage on the Web or in person at a site facility during the remaining study visits, given inconsistent ownership of or access to telephones and/or computers, variations in reading and technology literacy, and individual preferences for personal interactions with study staff. Participant choice for the mode of study visit is recorded. We elected to use this multimodal format to balance minimizing risk of bias (Hawthorne effect associated with facility-based data collection) with methods to optimize retention, recognizing that although TW have high rates of internet use [34], access can be inconsistent and reliance solely on Web-based data collection may threaten study retention.

Every 3 months, surveys will rotate length and format to maintain participant interest, although all surveys will utilize the same core measures selected from the baseline survey to ensure consistency across data collection visits. The app allows participants to report their HIV self-testing results and upload a photo for validation of results. Figure 3 displays the study app home screen, participant study timeline, and access to the survey and entry page for the home HIV self-test results.

Participants who experience HIV seroconversion during the study are asked to complete a facility-based visit for confirmation of HIV status (if HIV infection was identified during a Web-based visit) and referral. These participants are offered an additional follow-up visit 3 months after identification of seroconversion to assess uptake of referrals and engagement in the HIVCC (Figure 1). Participants are asked to complete a brief survey to answer questions about recent engagement in HIV care. This also serves as an opportunity for the study to provide additional referrals for any participant who has not yet accessed HIV care.

Figure 3. Leading Innovation for Transgender Women's Health and Empowerment study app: (a) home screen, (b) study timeline, and (c) access to survey and entry page for home HIV self-test results.



Measures

Baseline (Aims 1 and 2) and longitudinal surveys (Aims 3 and 4) are informed by the situated vulnerabilities framework [1]. Validated measures for use among TW or transgender populations have been incorporated into the survey [77], and wherever possible, we have selected measures previously tested with diverse populations to minimize cultural bias and to maximize comparability to other studies.

Survey Measures

All surveys, including facility-based and Web-based, are self-administered. We adapted the Rapid Estimate of Adult Literacy in Medicine – Revised, a brief literacy screening instrument used to assess an adult's ability to read common medical words, to include terms relevant to TW that are included in the survey (eg, pill, hormones, augmentation, and hepatitis) [78]. At the baseline visit, participants are asked to read 10 terms aloud; those who correctly read 7 or fewer are asked to participate in an interviewer-administered survey. Staff are also available to offer interviewer-administered surveys to participants with other needs that limit the participants' ability to self-administer (ie, visual impairment or discomfort with using a handheld tablet device).

Individual-level measures collect self-reported data on demographics, including zip code of residence, age, race, ethnicity, education, employment status, health insurance, housing, mobility, and history of detention/incarceration; gender affirmation surgery, care, and exogenous hormone use, including age of initiation, based on the US TransPop Survey [77]; sexual health history and access/uptake of HIV services (including postexposure prophylaxis; PEP and PrEP), based on the Centers for Disease Control and Prevention's (CDC's) National HIV Behavioral Surveillance [79]; and primary care, mental/behavioral health, social services utilization, and barriers and facilitators to care [14,15,80]. Substance use is measured by the Alcohol Use Identification Test Consumption Questions and the Drug Abuse Screening Test with additional measures for injecting drug use [81-83]; mental health symptoms including psychological distress (Kessler-6), posttraumatic stress disorder (PC-PTSD), and history of suicidal ideation and attempt [84]; and gender pride, affirmation, and dysphoria and transgender adaptation and integration assessing adjustment experiences specific to gender identity[85]. To assess Aim 4, which focuses on engagement of HIV-uninfected participants in the HIVPC, measures of linkage of HIV-uninfected participants to prevention services, types of services, retention in such services, and adherence to prevention interventions are also included [86].

Interpersonal measures include sexual relationships and behaviors measured via an adapted version of the AIDS-Risk Behavior Assessment [87,88] to assess self-reported, detailed partner-by-partner sexual behavior information by partner type and HIV status. This measure was updated for the potential incorporation of study data into mathematical modeling. Substance use in the context of HIV acquisition risk and "triggers" for sexual risk taking, which have been adapted for transgender populations to ensure gender-affirmative assessment of sexual risk, are included [89,90]. Measures of intimate partner violence (IPV) and nonpartner violence (NPV) victimization, respectively), including physical, sexual, and psychological violence and control, are based on an adaptation of the Conflicts Tactics Scale [91].

Structural-level measures include social marginalization and stigma, focusing on experiences of enacted and anticipated discrimination, were adapted from the Intersectional Discrimination Scale [92]. Social capital, with focus on participation in the local community; social agency; feelings of

trust and safety; neighborhood connections; and friends/family connections are included from subscales from the Social Capital Scale [93,94]. Interactions with the justice system and measures of immigration status, citizenship, and interactions with immigration detention are included. Finally, upon further recommendation by the CAB, an additional measure of food insecurity, adapted from United States Department of Agriculture Food Insecurity measures, is now included in the survey [95]. Surveys for participants with known HIV infection or who subsequently seroconvert include questions about engagement and retention in HIV care; initiation of antiretroviral therapy and adherence; CD4 and viral load testing; self-reported viral suppression, as defined by the National HIV/AIDS Strategy; and access to additional services for HIV infection [96-98]. Participants are also asked to provide consent to a medical record review for an extraction of their most recent confirmatory test, CD4, and viral load results.

Biological Measures

All HIV rapid testing is conducted following completion of the survey. HIV self-testing is performed by baseline participants including, for confirmation purposes, those who report known HIV infection. Participants self-administer the OraQuick self-test (OraSure Technologies) in the study facility during the baseline visit with support from trained study staff. This provides an opportunity for staff to train participants and answer any questions on the use of HIV self-test kits. HIV test results are available within 20 min. All participants with a positive HIV self-test undergo confirmatory testing according to CDC recommendations [99], and the patients are referred to a local and affirming HIV care facility of their preference.

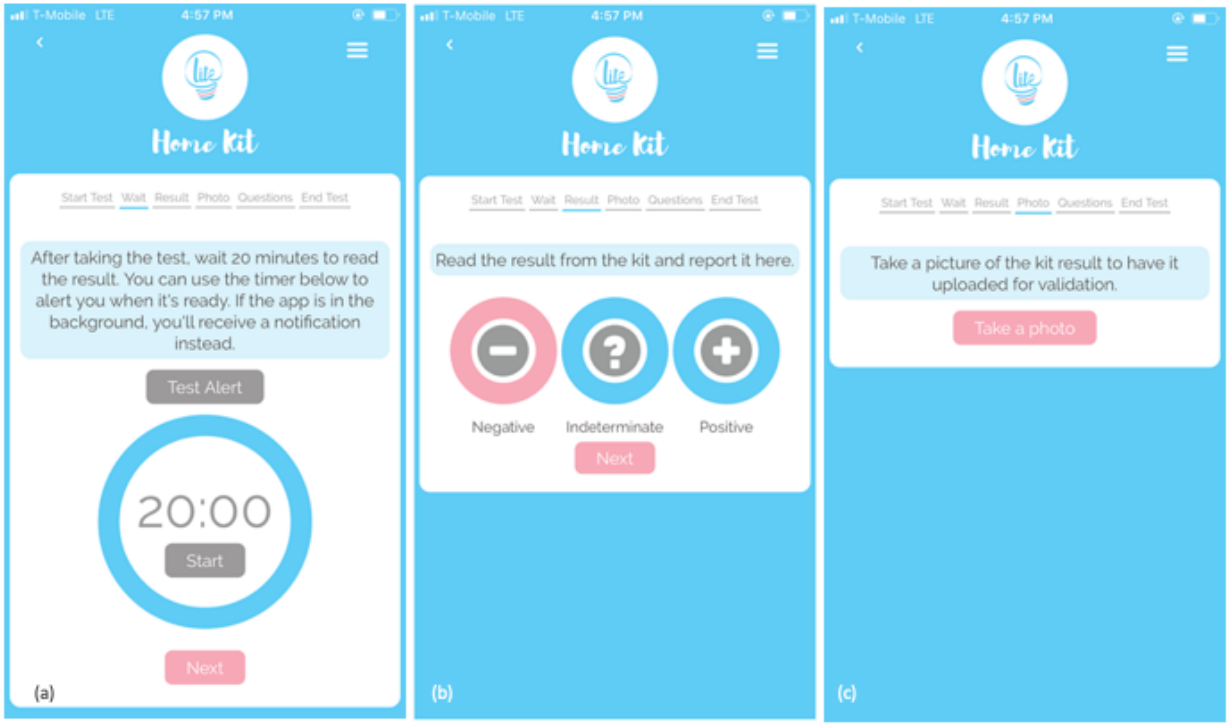
The HIV self-test is used for every 3-month visit (facility-based or Web-based) by cohort participants to support measurement of the primary outcome of interest (seroconversion). Participants completing Web-based study visits are asked to use the study app (Figure 4) or a secure URL to implement self-testing and report their HIV test results. The study app provides a video link to provide additional instructions to participants and a timer to guide implementation and prompt users to record the test result after 20 min. Participants are asked to interpret the results of the test and upload a photo of the test. Any participant with an unclear or otherwise invalid photo is asked to attempt to upload the photo again or repeat the HIV test. Auto notifications are sent immediately to the study staff for cohort participants who report a positive or indeterminate HIV self-test conducted at home; these participants are requested to come immediately to the study facility for confirmation and referral. This component of the app also includes measures of HIV self-testing acceptability for all participants who perform the HIV self-test on their own.

The oral point-of-care HIV test, OraQuick, was approved for self-testing use in the United States by the US Food and Drug Administration in 2012 [100]. OraQuick instructions are available in both English and Spanish. Test performance by untrained users is estimated to have a sensitivity of 99.9% and a specificity of 91.67% [101]. Participants are provided with the 24-hour OraQuick Support telephone number as well as the study coordinator (SC) number if participants have questions or have difficulty administering the test or interpreting the result. In addition to reducing staff time and involvement in HIV testing, self-testing has the promise of allowing TW to take greater control over their own health by putting the choice of when and where to test in their hands [102]. Study staff who can provide support may address the limitations of over-the-counter self-tests and improve testing behaviors. To our knowledge, there are no published data available on use of HIV self-testing or impacts of self-testing on undiagnosed infections among TW in the United States, although pilot studies have suggested high acceptability among TW [103].

Blood samples are collected at baseline and at 12 and 24 months. Plasma are collected and shipped to JHU to identify individuals with recent infection and estimate incidence at baseline by using a multiassay algorithm [104]. HIV incidence estimates can be greater than twofold lower in a longitudinal cohort than the underlying population [105,106] because of behavioral modification for those who enroll (Hawthorne effect) [58] and differential loss to follow-up by risk. We will also compare the individuals who appeared as recently infected at enrollment [107] with those who seroconverted during follow-up to determine if behavioral modification or differential loss to follow-up resulted in the difference in incidence [108]. In addition, the biospecimens at baseline and those collected during follow-up will be stored for future phylogenetic analysis, until additional funding become available.

Self-collected specimens to test for STIs are collected from all participants at baseline and at 12- and 24-month visits, including among HIV-infected baseline and HIV-uninfected cohort participants. Urine samples as well as swabs collected at anorectal and vaginal (for those with vaginoplasty) sites will be self-collected to measure presence of gonorrhea and chlamydia infection. Serum treponemal syphilis testing and rapid plasma reagin (RPR) testing with quantitative RPR titers are used to test for syphilis infection, per local protocols. STI testing is conducted locally at facility-based visits. These STI tests serve as a biologic proxy measure for HIV risk.

Figure 4. HIV testing component of the study app: (a) HIV test timer, (b) HIV test results entry, and (c) photo upload for HIV test validation.



Recruitment Process Measures

Aim 1 focuses on the efficiencies of recruitment methods. Data on the number of banner ads and postings, impressions (number of online views), and click throughs (number of times the ad was clicked) and data on the number of visits to the study website will be collected for all technology-infused recruitment. For recruitment from gender-affirming events, the number of events, number of participants at each event, and number of candidates accessing study information will be collected. For peer referral, information on the number of unique coupons provided to each participant, number of declined coupons, and number of unique coupons returned to the study staff will be collected. For clinic-based referral, the number of unique TW clients utilizing the clinic during the recruitment period and number of referrals or fliers distributed will be collected. For all recruitment methods, time from recruitment initiation to enrollment, costs associated with recruitment, the number of scheduled enrollment appointments, and the numbers of eligible participants (by HIV status) will be collected by recruitment method. Baseline survey participants will be asked to report how they learned about the study.

Quality Assurance/Quality Control Plan for All Study Phases

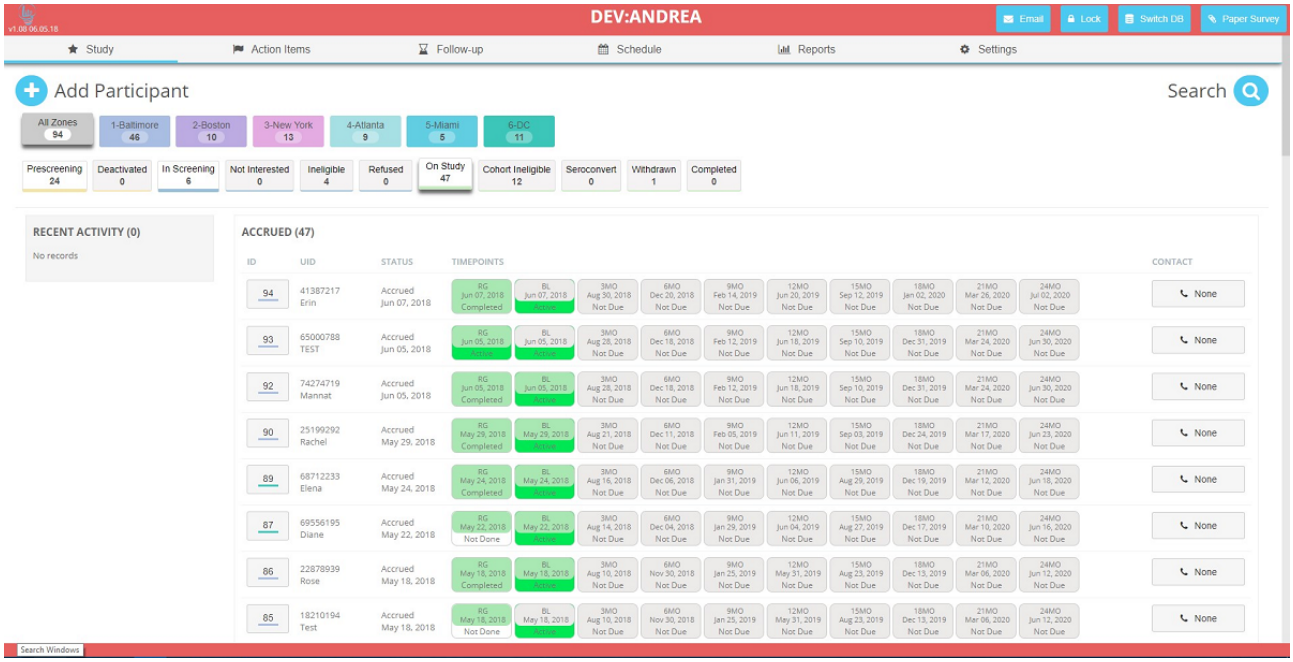
Before study implementation, a study manual of procedures was developed, which included the full study protocol as well as study background, design, organizations, recruitment techniques, informed consent, clinical procedures, participant safety, instructions for entering data and using tablets, follow-up procedures, and study definitions. The manual of procedures was then adapted to each site for additional details related to unique aspects of the facility where research is conducted. Updates and clarifications are made as necessary over the course of the project, with revisions available to all staff. All staff are required to undergo training on the overall research objectives and protocol, transgender health, and HIV, along with human subjects training. Clinical staff are required to complete additional training on clinical procedures, confidentiality and privacy, and Good Clinical Practice. Refresher training is scheduled on an annual basis. Weekly calls are held with SCs at each site to discuss adherence to the study protocol, enrollment progress, and experiences with retention.

To ensure consistency in the survey data collection and minimize social desirability bias, we use a computer-assisted self-interview methodology, which includes self-administered tablet-based surveys during facility-based visits and self-administered app-based or Web-based surveys during Web-based study visits. The use of the self-administered tablet-based survey at the facility-based baseline visit allows participants to become accustomed to the Web-based survey and ask for assistance from the study staff. The survey instruments were pilot tested before implementation, and logic checks and skip patterns are built into the program to minimize errors in data capture. Security features of the Web-based and app-based survey allow for data to be saved regularly as participants advance through the survey questions, preventing unintentional loss of data should there be a loss of internet connectivity. Data are reviewed weekly to check for consistency in the data capture processes and assess missingness of data.

Participant Tracking

Cross-sectional and cohort participants are tracked using a Web-based, Health Insurance Portability and Accountability Act–compliant system hosted by JHU central information technology which allows for facility-based data collection and participant tracking over the course of the study (Figure 5). This system has been used in other prospective studies by the JHU team [109].

Figure 5. Participant database (note: image is a development interface and displays test subjects, not actual participant data).



The Web-based tracking system is customized and configured by the study team to fit the study protocol. Each site has role-based and site-based access to their data, with JHU having full administrative access to all data. It has also been expanded to provide the additional cohort participant app, with an optional URL platform for nonsmartphone users. At enrollment, a unique identifier is generated for participants to log in and access the app and associated surveys. To assist with the recall of the identifier, cohort participants are provided with a study gift (eg, cellphone cardholder) with a study card that includes their study identifier. SCs assist cohort participants with download and installation of the app during enrollment. Participants who encounter problems with subsequent installation (if phone is replaced) or log-in are encouraged to call the study telephone number for support. The participant app is locked on the device once installed, and it requires the entry of the assigned study ID for it to be accessed. The app is Global Positioning System (GPS) enabled, although participants may opt out, to allow for measurement of participant mobility over the duration of the study. The tracking system issues automated push notifications and SMS text messages to the participants' device for follow-up visit reminders.

All data collected by the tracking system and participant app are encrypted in transit from the device to the server. All the identifying information collected from participants is stored encrypted within the database using the AES 256 bit protocol. Only the research staff requiring access to identifying information for retention purposes has access to protected health information through the tracking system.

Study Retention

Meticulous tracking and retention procedures increase the likelihood that attrition is random and not systematic during study implementation. We use tracking and retention procedures that were proven effective in previous studies. The SC at each site devotes at least 50% time to recruiting and tracking subjects. The SC and other research staff collect and regularly update extensive email/phone/social media contacts, as well as the addresses and contact information of the 3 people that participants believe could help us locate them and will telephone/email/text participants to remind them of their appointment. Automated study visit reminders are also built into the participant tracking system and study app.

Culturally appropriate stepped financial incentives are also provided at each follow-up to encourage continued participation. Depending on the site, additional nonmonetary strategies to improve retention include the following: (1) an anonymous raffle for study participation, (2) provision of links to other non-HIV gender-affirming care and services available during facility-based visits and on the study website and app, (3) a Facebook page on which participants can communicate with each other and staff and post events, and (4) retention events focused on providing non-HIV services of interest (eg, legal name and gender-marker change workshops for identification documents, spa days, and other social events). Retention events are typically held within the community to keep participants engaged in the project.

Facilities provide a range of times of day and days of the week for participants to come to their assessment visits, including evening hours and weekends to support participation by individuals who work or are in school full time. Clinical partners also have excellent reputations within their communities, and they are known for being nonstigmatizing and ensuring privacy and confidentiality, which assists with retention. We also have an extensive network of transgender-focused organizations and clinical care providers in each of our partnering metropolitan areas who serve as referral centers for health needs. Finally, we endeavor to hire study staff who are from the TW or lesbian, gay, bisexual, and transgender community and who have nursing or public health experience, to ensure cultural competence and optimize acceptability of the study.

Study retention is operationally defined as not missing more than 3 consecutive study visits. After 2 missed visits, SCs initiate the retention protocol to track participants through individual and friend/family contacts and calls to local facilities to identify potential incarceration. Participants who express a desire to prematurely exit the study are asked to complete a participant withdrawal questionnaire (on the Web, by phone, or in person) to assess basic characteristics at study exit (eg, HIV status and PrEP use), reason for withdrawal, and whether additional referrals are needed. The study team assesses whether the reason for withdrawal can be addressed, and then the study team will offer resolution, within the limits of the protocol, to the participant. Cohort participants who are lost to follow-up or who have previously withdrawn and request to reenter the study are screened and reassessed for eligibility, and if the timeline allows, they are administratively considered for reenrollment.

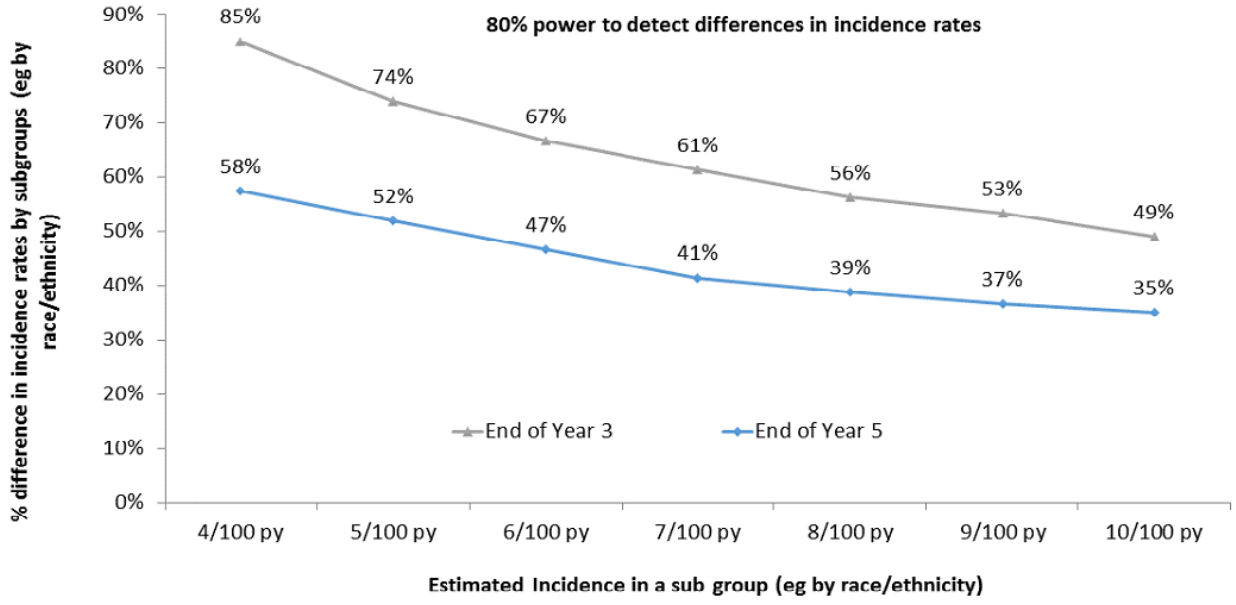
Statistical Considerations

Sample Size

We anticipate that 1750 individuals will be screened (approximately 350 per city) from years 1 to 2. Assuming 10% of those screened are ineligible and have an HIV prevalence of 30%, TW enrolled at the end of Year 2 will include 1100 HIV-uninfected TW (approximately 220 per city) and 475 HIV-infected TW in the baseline, cross-sectional comparison group.

We conservatively estimated that 700 pys of follow-up accumulated from Years 1 to 2 during enrollment. Incorporating a loss of 15% of follow-up time per year (from a combination of loss to follow-up and mortality), we estimate that we will accumulate 935 pys, 795 pys, and 676 pys in Years 3, 4, and 5, respectively (>3000 pys total). To compare the incidence of 2 subgroups (eg, incidence by black vs nonblack race), assuming 2-sided test statistics and 5% Type 1 error 80% power, we have sufficient power (80%) to detect public health–relevant differences in HIV incidence by various participant characteristics (Figure 6).

Figure 6. Power to detect public health–relevant differences in HIV incidence by subgroups. py: person years.



Sample Size Considerations

HIV incidence in TW is the primary study outcome of interest. With respect to the baseline, cross-sectional incidence estimate, a sample of 1575 individuals at baseline with 30% prevalence and estimated cross-sectional 8% incidence would identify 37 “recently” infected individuals with a 95% CI of 4.7-11.5 using the validated algorithm [104].

Study attrition is tracked using data visualization techniques, stratifying important metrics over time (such as the number enrolled and proportion lost to follow-up) by site. Monthly updates to these figures will help to detect problems and initiate a timely response to ensure at least 1000 TW are enrolled in the cohort and to reduce loss to follow-up. Statistical analyses of attrition will be conducted, including a comparison of demographic characteristics, social factors, and HIV risk behaviors among those retained versus lost to follow-up. Survival analyses will be used to investigate factors associated with loss to follow-up.

Analytic Plan

Data management and statistical analysis are led by statisticians and data managers in the John Hopkins Bloomberg School of Public Health (JHSPH) Statistics in Epidemiology (STATEPI) group (which serves the North American AIDS Cohort Collaboration on Research and Design and the Multicenter AIDS Cohort Study / Women’s Interagency HIV Study

Combined Cohort Study, which are longitudinal cohorts of adults with, and at-risk for, HIV infection) with oversight by study investigators (ALW, SR, and KNA). Analyses essential to the proposed aims include tracking and investigations into attrition, comparison of HIV-infected and HIV-uninfected TW at baseline, both HIV incidence and time-to-event analyses to better understand drivers of HIV transmission, and serial cross-sectional looks at the HIVPC and HIVCC over calendar time.

Statistical analysis throughout the study addresses the overarching specific aims and hypotheses. Aim 1 analyses focus on exploring optimal recruitment methods and the efficiency of each method. Data visualization techniques are being utilized to compare efficiency of recruitment methods in terms of process measures of time, cost, and response rates. Additional descriptive analyses compare quantitative measures of acceptability and will also assess diversity and potential biases of the samples recruited, in terms of demographics, risk behaviors, and HIV status. Differences are not statistically compared across recruitment methods, given heterogeneity of recruitment methods and process measures.

Aim 2 analyses include descriptive statistics to compare demographic and behavioral risk profiles among HIV-uninfected and HIV-infected baseline participants as well as to assess baseline HIVPC and HIVCC among HIV-uninfected and HIV-infected participants, respectively. Log binomial models (or, when such models fail to converge, we will approximate with Poisson regression models with robust variance) are used to estimate HIV prevalence ratios and 95% CIs for demographic and risk characteristics; subgroup analyses will be conducted, stratified by site. Latent class analysis will be further used to explore profiles of HIV-infected and HIV-uninfected participants at baseline [110]. Statistical analysis is completed using Stata version 14 (StataCorp) [111], Mplus (Muthen & Muthen) for latent class analysis, and RDS Analyst in R software (University of California, Los Angeles) for visualization of peer-recruitment networks (including homophily and depth).

Aim 3 analyses will focus on differences in HIV incidence during follow-up (and 95% CIs) among the HIV-uninfected cohort will be estimated using Poisson regression models to investigate important predictors, including (but not limited to) age, race/ethnicity, and geographic location. Observed HIV incidence from the cohort will be compared with baseline cross-sectional incidence to assess for differences in incidence and potential mechanism for such differences (eg, differences in participant profiles and behavioral modification). Time-to-event survival models will be used to estimate the risk of HIV seroconversion for the predictors. A scan statistic will be used with the zip code of residence and GPS data to detect seroconversion event clusters in time or space (or both) for identification of potential microepidemics. The scan statistic is commonly used to identify the most likely cluster location, where a significant *P* value ($P<.05$) indicates that it can be concluded that the most likely location of clustering was unlikely under test assumptions [112]. Statistical analyses will be performed using Stata 14 (StataCorp) and SatScan (Kulldorff).

Analyses for Aim 4 will focus on the steps in the HIVPC and HIVCC are investigated among HIV-uninfected and HIV-infected TW, respectively, using a serial cross-sectional approach to determine trends in these important frameworks. To make these estimates most useful for policy and program, the steps are estimated among those under observation in specific calendar years (ie, in 2019, 2020, and 2021).

For analytic refinements, we will make use of modern missing data techniques [113], with particular emphasis on multiple imputation methods, which provide a useful umbrella for handling different forms of missing data including coarsely measured [114] or mismeasured [115] variables. Adaptation of these methods to survival analyses will be similar to techniques implemented in R/MICE and SAS/IVEware [116-118]. These methods are appropriate when data are not missing at random and missing data occur in multiple variables simultaneously. For evaluating the impact of unmeasured confounders, we will make use of sensitivity analyses techniques [119] previously used to determine the impact of unmeasured confounders by the strength of the confounder.

Participant Protections

Scientific measurement of HIV infection, as well as gender identity, sexual identity and behavior, and stigma, is inherently sensitive in nature. All study activities are developed with attention to protection of participant privacy and confidentiality and in discussions with the study CAB. All participant study data are retained separately from participant identifiers; only study staff responsible for scheduling or referrals have permissions to access participant identifiers. The electronic data system has been developed with careful attention to security, including password protection and no obvious information that the app is developed for TW or for HIV research. Participants are provided with clear instructions on how to use, discretely store, and report results from the HIV self-test as well as how to contact the study staff in the event of a positive test result. Given concerns of stigma and discrimination, only referrals to clinics or community based organizations that have been vetted and determined to be gender affirming are provided. Finally, the CAB has been consulted throughout all phases of the study to ensure acceptability of methods among the TW community. Study activities follow a single centralized Institutional Review Board (IRB) procedure and have undergone review and approval by the Johns Hopkins School of Medicine IRB. All collaborating organizations and institutions rely on this approval.

Scientific Rigor and Reproducibility

Rigor and reproducibility are ensured throughout all phases of the study by the stringent application of the scientific method to minimize bias in design, methodology, analysis, and interpretation of results, and they will follow methods successfully used by *MACS*, *WIHS*, and *LifeSkills* cohorts [88,120,121]. These methods include but are not limited to the following: inclusion of a baseline, cross-sectional sample of HIV-infected TW against which the risk profile of the HIV-uninfected cohort may be compared; sample size estimation based on power to detect differences in incidence across subgroups and to detect differences estimated during cross-sectional incidence testing and longitudinal measures of

incidence; attention and efforts to maximize study retention; attrition analysis as well as assessment and methods to address missing data; use of statistical measures that have demonstrated applicability in HIV incidence estimation and descriptive analysis; and documented quality assurance/quality control by the data collection/management group; as well as standardized methods utilized by the JHSPH *STATEPI* group. Several steps are undertaken to ensure reproducibility of the study results, including publication of the study protocol and methodology and data archiving of deidentified data for public use; a scientific steering committee, composed of the multiple PIs, the PIs of the site cohorts, and the primary data coinvestigators; a concept sheet process to allow for input from all and to create opportunities for research by all investigators, including external investigators and junior faculty members; development of analytic summary files to ensure key variables are put into a scientifically appropriate form and used consistently in analyses; and development of analytic standards for analyses, including adjustment for differences by cohort, sensitivity analyses stratified by study site.

Results

Formative research was conducted between August 2017 and January 2018, and findings have been described elsewhere [59,66]. These included 5 Web-based synchronous computer-mediated focus groups conducted in English (n=33) and 2 Web-based synchronous computer-mediated focus groups that were conducted in Spanish (n=8). The geographically diverse sample, which spanned all 6 cities, had a mean age of 41.1 (SD 13.6) years; 66% (27/41) of the participants identified as people of color, and 29% (12/41) of the participants identified as Hispanic/Latina. Participants provided input into the study name and branding, recruitment materials and messaging, and considerations for implementation of HIV self-testing. Participants also described past experiences of HIV research participation, which largely described the social and economic factors that shaped their experiences. Barriers to and negative experiences in HIV research participation included limited research opportunities, mistrust, fear of mistreatment, concerns about safety and confidentiality, competing priorities, and HIV stigma. Facilitators to and positive experiences with HIV research participation included peer involvement and engagement, monetary and nonmonetary incentives, flexibility and choices, multiple modalities and methods, and transcenteredness [66].

In March 2018, the cohort was launched at the Baltimore and Boston sites, followed by launches of the cohort in the remaining cities in April and May 2018. This staggered approach was established to allow for any troubleshooting of study implementation procedures, the CTMS, and study app before the full launch in other sites as well as for final IRB reliance agreements to be established. As of March 20, 2019, 795 TW were screened and 739 TW were enrolled in and completed the baseline study visit (median age 32 years, interquartile range; IQR 25-42 years). Majority of the participants are racial/ethnic minorities, with 45.1% (333/739) of the participants identifying as black and/or 27.8% (206/739) identifying as Hispanic/Latinx. Of these baseline participants, 206 (27.8%, 206/739) were found to be living with HIV at baseline and 480 (64.9%) were HIV-uninfected and met behavioral risk criteria and were enrolled in the cohort (cohort median age: 29 years, IQR 24-37 years). This contributed to a total 245.4 pys in the cohort as of March 2019. A total of 17% (126/739) of the baseline participants were identified with lower levels of literacy, requiring interviewer-administered surveys and HIV tests, as well as in-person visits. Other participants have requested in-person visits, reportedly for the purposes of having a safe and private place to participate in study activities, comfort in having a staff member perform or be present for HIV testing, or because the participant wanted to see or spend time with study staff.

Baseline participants have entered the study through a variety of recruitment methods, including peer referral (38.9%, 288/739), referral from a health facility (40.0%, 296/739), referral from a community-based organization (12.0%, 89/739), study flier (10.9%, 81/739), Facebook (7.9%, 59/739), dating apps (4.0%, 30/739), or other websites (4.0%, 30/739), such as Craigslist, Backpage, and Eros. However, study recruitment has progressed overall at a rate lower than expected and with lower proportions recruited online than anticipated. The use of advertising campaigns in dating apps to recruit participants appeared to reach a large number of individuals (1,390,827 impressions and 11,629 clicks on the study website during geotargeted campaigns via 1 dating app), but it resulted in only 24 enrollments to date. This is likely attributable to the fact that TW may use dating apps that are developed for heterosexual populations, as well as people in same sex relationships, with no single app being uniquely for or in high use by TW, thus limiting the number of those who can be reached through advertisements via these apps. Furthermore, challenges in communication with dating app representatives, low transparency and barriers to recruitment data, and cost associated with recruitment via dating apps suggest that these are not efficient methods for recruitment of TW for research. Given these challenges, we have broadened recruitment to advertising campaigns via Facebook, Reddit, and Google Ads, as well as sharing information about the study through media interviews [122-125].

Discussion

This study is responsive to increasing research interest in technology-enhanced methods for cohort research, particularly for hard-to-reach populations. The cohort utilizes innovative methods that harness technology alongside traditional methods and facility-based visits to develop the first multisite US cohort to assess HIV risk among one of the most affected populations. Study findings have important implications for informing future HIV prevention and care research, including identification of optimal recruitment and retention methods, estimating HIV incidence and identifying risk factors for HIV acquisition, and ultimately informing the development of acceptable HIV prevention and care efforts for TW in the United States. Importantly, the diversity of literacy, technology use, and overall socioeconomic situations in this sample of TW highlights the need to balance study rigor with use of flexible methods to

ensure that with increasing technology, those living in the most vulnerable contexts are not excluded from research.

Limitations of the study must be recognized. First, the sample size is relatively small compared with other national cohorts that comprise larger, less stigmatized populations. However, the use of multiple partnering sites with strong ties to the TW community, partnership with a CAB, and use of mixed-format recruitment and data collection methods are anticipated to encourage recruitment and retention across sites. As additional funding is identified, new sites and organizational partners may also be added. Although the pooled contribution of cohorts from multiple sites adds strength to the study, pooled results can provide misleading or overly smoothed inferences. Our analytic "best practices" protocol includes examining data for each cohort to understand the magnitude of heterogeneity in estimates. Statistical methods for determining cohort interactions and combining pooled results [113] will be utilized. Furthermore, we will continue to use sensitivity analyses to examine the influence of individual cohorts on specific results, such as omitting cohorts systematically by use of jackknife methods with unequal partitions [114]. Finally, the use of cross-sectional incidence testing has been incorporated into the study to support and assess longitudinal incidence estimation as well as to assess for any Hawthorne effect associated with participation in the cohort.

This study establishes a multisite, longitudinal cohort of TW in eastern and southern United States, targeting 6 high-risk metropolitan areas: Baltimore; Washington, DC; Boston; New York City; Atlanta; and Miami, and it is now one of the largest cohorts specifically comprising TW in the United States. The goal is to characterize risk factors for HIV infection, access to biobehavioral HIV prevention methods, and linkage to care for those who HIV seroconvert for the purposes of informing evidence-based and acceptable interventions to reduce HIV incidence for this at-risk population. The cohort will include a racially, ethnically, and culturally diverse sample of TW, supported by technology-based recruitment and retention methods. The study is designed to (1) answer methodologic questions about appropriate and effective recruitment and retention methods for TW, as well as potential biases in these methods; (2) provide HIV incidence estimates and, through the use of both cross-sectional and longitudinal incidence measures, assess potential influences on incidence estimations; (3) identify individual social and structural risk factors for HIV acquisition; and (4) evaluate engagement in the HIVPC and HIVCC among HIV-uninfected and HIV-infected TW. We anticipate that the cohort study will serve as a platform upon which pilot interventions, studies of sexual partners, cohorts of TW youth, additional geospatial and phylogenetic analysis to further contextualize hot spots, mathematical modeling to assess the impact of promising interventions, and analysis of the role of exogenous hormone use in HIV infection can be built. Collectively, these findings will inform optimal components of promising interventions to reduce HIV incidence among TW.

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Authors' Contributions

The following are members of the collaborative author, American Cohort to Study HIV Acquisition Among TW (LITE): Sari Reisner (multiple PI; Harvard University, BCH); Andrea Wirtz (multiple PI; JHU); Keri Althoff (JHU); Chris Beyrer (JHU); James Case (JHU); Erin Cooney (JHU); Oliver Laeyendecker (JHU); Tonia Poteat (University of North Carolina); Kenneth Mayer (Fenway Health); Asa Radix (Callen-Lorde Community Health Center); Christopher Cannon (Whitman-Walker Health); W David Hardy (Whitman-Walker Health); Jason Schneider (Emory University and Grady Hospital); Sonya Haw (Emory University and Grady Hospital); Allan Rodriguez (University of Miami); Andrew Wawrzyniak (University of Miami); and the LITE CAB, including the following individuals: Jennifer Lopez, Sherri Meeks, Sydney Shackelford, Nala Toussaint, SaVanna Wanzer, and Joseph Zolobczuk, as well as those who have remained anonymous. ALW and SLR developed the study concept; TP, AR, KNA, CC, AW, EC, and KM provided extensive input to the original grant submission and/or the protocol manuscript; ALW wrote the first draft of the manuscript; and all authors reviewed and provided scientific input to the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the National Institutes of Health.
[PDF File (Adobe PDF File)174 KB - resprot_v8i9e14704_app1.pdf]

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Abbreviations

BCH: Boston Children's Hospital
CAB: Community Advisory Board
CDC: Centers for Disease Control and Prevention
CFAR: Centers for AIDS Research
CMC: computer-mediated communication
GPS: Global Positioning System
GSN: geosocial networking
HAHSTA: HIV/AIDS, Hepatitis, STD, and TB Administration
HIVCC: HIV Care Continuum
HIVPC: HIV Prevention Continuum
IQR: interquartile range

IRB: Institutional Review Board
JHSPH: John Hopkins Bloomberg School of Public Health
JHU: Johns Hopkins University
LITE: Leading Innovation in Transgender Health and Empowerment
PI: principal investigator
PrEP: pre-exposure prophylaxis
pys: person years
RDS: respondent-driven sampling
RPR: rapid plasma reagin
SC: study coordinator
SMS: short message service
STATEPI: Statistics in Epidemiology
STI: sexually transmitted infection
TW: transgender women

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Protocol

Remotely Supervised Home-Based Intensive Exercise Intervention to Improve Balance, Functional Mobility, and Physical Activity in Survivors of Moderate or Severe Traumatic Brain Injury: Protocol for a Mixed Methods Study

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Abstract

Background: Traumatic brain injury (TBI) may impact an individual physically, cognitively, socially, and emotionally. Poor balance, reduced mobility, and low daily physical activity often will require ongoing physical rehabilitation intervention. However, face-to-face specialized physiotherapy is not always accessible for individuals living in rural settings.

Objective: We will answer four questions: (1) What is the feasibility of a remotely supervised, home-based, intensive exercise intervention with survivors of moderate and severe TBI? (2) Does the frequency of remote supervision have an impact on the feasibility of completing a home-based intensive exercise program? (3) Does the frequency of remote supervision impact balance, functional mobility, and physical activity? (4) What is the lived experience of remote supervision for both survivors and caregivers?

Methods: Four participants will complete two intensive, 4-week (five days per week) home-based exercise interventions remotely supervised via synchronous videoconference. Each exercise intervention will have a goal of 160 to 300 repetitions or 60 minutes of tailored exercises to promote neuroplasticity and be defined as an intensive home-based exercise intervention. An alternating single-subject design will allow for the comparison between two frequencies of remote supervision, once weekly and five times weekly. Daily repeated outcome measures, pre- and postintervention outcome measures, and 1-month follow-up outcome measures will be collected to explore the effect on feasibility and physical variables. Daily outcome measures include step count and Five Times Sit-to-Stand test. Pre-post measures include assessment of quiet stance and the Community Balance and Mobility Scale. A semistructured interview will be completed at the end of each intervention segment to document the lived experience of both survivors and their study partners. Finally, five questionnaires will be used to understand the overall experience: the Mayo-Portland Adaptability Inventory-4 Participation Index, Satisfaction With Life Scale, Fall Efficacy Scale-International, Interpersonal Behavior Questionnaire, and System Usability Scale. Data will be analyzed following traditional single-subject methods of analysis.

Results: Ethics approval was received from both the Bruyère Research Institute and University of Ottawa review boards in March 2019. Recruitment is underway.

Conclusions: The proposed intervention is complex in nature due to the involvement of multiple technology sources and the inclusion of a complex dyad (survivors and caregivers) in a community setting. This type of research is timely given that alternative

methods of physical intervention delivery are needed to facilitate gains in balance, mobility, physical activity among TBI survivors with limited access to clinical care, and the quality of the patients' experience.

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KEYWORDS

telerehabilitation; physical activity; traumatic brain injury; home-based exercises; accessibility

Introduction

Background

A traumatic brain injury (TBI) can impact an individual physically, cognitively, socially, and emotionally, as described by the Ontario Neurotrauma Foundation [1]. These impairments can become chronic, influencing the quality of life of an individual throughout their life span. One-third of military personnel who survived a moderate or severe TBI have continued issues with activities of daily living even up to 14 years postinjury [2,3]. Physical deficits can present as poor balance [4], reduced mobility, and low daily physical activity [5]. These impairments may lead to decreased social participation [6], increased fear of falling [7], and may invoke social isolation [8].

Physical rehabilitation professionals, such as physiotherapists, can influence the recovery of these deficits [9,10], which may positively influence daily function [7]. Traditional face-to-face outpatient physiotherapy sessions are usually completed in-clinic, in-person with a therapist; however, this option is not always accessible to the affected individual. Inequities can be associated with geography, financial barriers, or acceptability [11]. A lack of available knowledgeable professionals in rural communities, increased travel cost and travel time to urban centers, and injury characteristics are examples of barriers for survivors of moderate or severe TBI living in rural communities [7,12,13].

For these reasons, it is crucial to investigate alternative methods of treatment delivery that could impact the accessibility of specialized physiotherapy services. Synchronous remote supervision refers to a form of remote supervision, such as videoconferencing, which allows patient information to be received and recorded in real time by the supervising therapist, and for the therapist to provide immediate feedback [14,15]. Previous studies have assessed the usability of telerehabilitation for the neurologically impaired population and found it to be "as feasible as usual care for upper extremity function in stroke, TBI, and MS [multiple sclerosis]" [16]. Balance interventions delivered remotely by telerehabilitation were also shown to be effective for people with neurological diagnoses [17,18].

To facilitate neuroplasticity, increasing patients' daily physical activity participation and the number of exercise repetitions they perform are key factors [19], and must be included in any home-based exercise program. Most effective exercise programs for balance, functional mobility, and physical activity for TBI survivors range between 16 and 20 sessions completed in 4 to 6 weeks [10,20-23]. These exercise programs were delivered face-to-face or as a home program without remote supervision. Therefore, we are still uncertain of the effect of frequency for remotely delivered programs.

Exploring the effect frequency of supervision has on different outcomes is needed to develop accessible and effective interventions for this population. A recent study by Lacroix et al [24] explored the dose-response relationship between static balance outcomes and supervision in older adults. They found increased effects with supervision compared with no supervision. They also showed that a low number of supervised sessions (mean 6.7 sessions) was enough to have a positive effect on outcomes, but not as much as full supervision (mean 30 sessions). This indicates that having supervised sessions is important for improving motor skills. However, we are still uncertain of the specific amount of supervision needed to have an impact on physical impairments while remaining feasible for survivors. Minimal research has been done in this area for TBI survivors. It is feasible for this population to independently complete a community exercise program [25]; however, the optimal frequency of remote supervision that will positively impact physical outcome measures is unclear.

Objectives

This study will determine the feasibility and effectiveness of two frequencies of remote supervision for a home-based intensive exercise intervention (daily and weekly supervision) for military or veteran survivors of moderate or severe TBI. Four main questions will be investigated:

1. What is the feasibility of a remotely supervised home-based intensive exercise intervention with survivors of moderate and severe TBI?
2. Does the frequency of remote supervision have an impact on the feasibility of completing a home-based intensive exercise program?
3. Does the frequency of remote supervision impact balance, functional mobility, and physical activity?
4. What is the lived experience of remote supervision for both survivors and caregivers?

We hypothesize that a remotely delivered exercise program targeting balance, mobility, and increased physical activity will be feasible and that frequency of supervision will have an impact on the effectiveness of the intervention. We also hypothesize that the dyad (survivor and caregiver) will report a satisfactory experience.

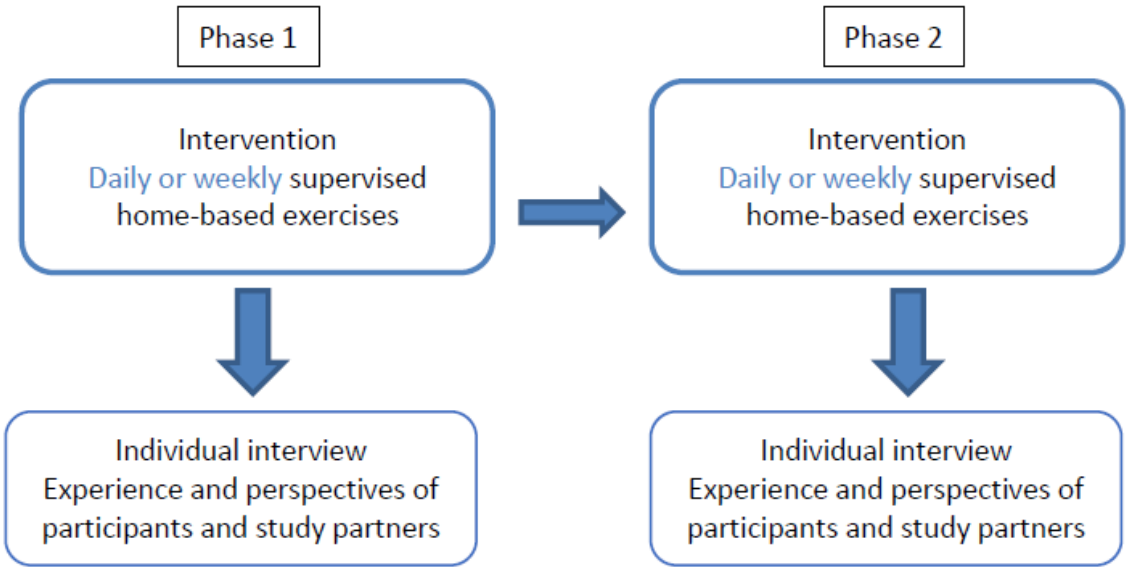
Methods

Overview

This study will follow a sequential explanatory mixed methods intervention approach (Figure 1) [26]. Qualitative observations collected via semistructured interviews will help interpret and better qualify information stemming from the quantitative data.

A single-subject design is often used to compare different interventions in clinical settings [27-29] and provides a way to explore the feasibility and potential effectiveness in the early stages of investigating a new intervention. An alternating single-subject design will allow for comparison between the two frequencies of remote supervision. The phase sequence determined a priori will include baseline (6 data points), intervention 1 for 4 weeks (20 data points), a 4-week washout period, intervention 2 for 4 weeks (20 data points), a postintervention phase (3 data points), and a 1-month follow-up phase (1 data point). A 4-week washout period will be added to mitigate the effects of the first intervention on the second intervention. During this period, the participants will be asked not to perform any of the specific exercises from the intervention program. Replication across four participants will help establish if there is a causal relationship.

Figure 1. Sequential explanatory approach demonstrating the phases of the remotely supervised home-based interventions differing in supervision frequencies. A crossover design will be used; two participants will begin with daily supervision and two participants will begin with weekly supervision.



Participants

Four survivors of moderate to severe TBI aged 18 to 64 years and their respective study partners will be recruited from the community via recruitment posters and videos. Participants will be eligible if they report a diagnosis of a moderate or severe TBI a year or more ago. This diagnostic can be defined as a score of 12 or less on the Glasgow Coma Scale [30], time spent in an in-patient unit, loss of consciousness with trauma, or presence of posttraumatic amnesia. To be included, participants must speak English or French and live in the community (not in the hospital or long-term care facilities). The ability to stand independently for a minimum of 2 minutes will be required. Participants will be asked to confirm this on the screening call and will be assessed for 2 minutes stance at the first assessment session. In addition, the TBI survivors will need a consenting study partner. The relationship between study partner and participant can be of a personal nature, such as caregiver, family member, personal support worker, or friend willing to participate with the survivor for the entire study.

Potential participants will be excluded if they report symptoms of vertigo, measured by questions from the Dizziness Handicap Inventory [31], or are unable to use the videoconferencing system.

Exercise Intervention

Interventions will take place in the participants' homes. Five face-to-face visits at the Bruyère Research Institute in Ottawa, Canada, will take place for assessment purposes. All exercise interventions will be completed remotely.

A familiarization session during the first face-to-face visit at the Bruyère Research Institute will mark the first day of the baseline phase. The participant and study partner will be trained on the use of the activity tracking device and the videoconference platform. Education on safety precautions during the home-based exercise intervention session will be provided (ie, wearing proper shoes, removing clutter, having enough space to move, having a chair near to take breaks when required, instructions in case of presence of dizziness, injuries, or falls). The exercise intervention objectives will be discussed with the dyad, such as "the goal of this exercise intervention is to increase your physical activity levels, improve your balance and mobility by spending 30 to 60 minutes per day exercising. The goal is to reach a minimum amount of repetitions per session ranging between 160 and 300 repetitions." Questions related to individual abilities, goals, motivation, and adherence strategies will be asked to tailor the intervention to each participant. Collaboration with the study partner will take place to tailor the daily diary log and facilitate its completion. A

participant manual, including daily exercises, safety precautions, and technology information, will be provided to each study dyad. TBI survivors assisted by the study partner will be asked to complete a daily log including step count and the Five Times Sit-to-Stand (FTSTS) test [32,33].

The four participants will complete two intensive, 4-week (five days per week), home-based exercise interventions remotely supervised via synchronous videoconference. Participants will be supervised via videoconferencing daily or weekly for the entire proposed intervention period. During the weekly remote supervision intervention, remote supervision will be provided on Mondays; for the remaining days of the week, participants will complete the intervention aided by their study partner, but unsupervised by the researcher. Each participant will be emailed a link to start the videoconference intervention 15 minutes before starting the intervention, and the study partner will facilitate connection with the therapist. The therapist in charge will collaborate with the dyad to ensure proper positioning of the camera and safe environment.

A trained and registered physiotherapist with over 10 years of experience in rehabilitation of TBI will provide all remote supervision sessions via the Ontario Telemedicine Network. Each participant will be asked to complete the exercise intervention at the same time of the day. Individual exercise sessions will be structured and tailored to each participant as defined in the familiarization session. The exercise intervention will consist of two to four exercises targeting essential components of dynamic balance, weight shifting, reaction time, and postural control (Table 1). As an example, sit-to-stand, side stepping, lunges, squats, tandem walking, and single-leg stance could be included in the exercise intervention (Multimedia Appendix 1). These specific exercises were chosen because they were included in previous programs targeting dynamic balance in TBI survivors [5,10,20-23]. Exercises will be completed 1 minute at a time, for a total of 10 minutes per specific exercise. When possible (ie, with the sit-to-stand exercise), the number of repetitions of the exercises will be recorded by the therapist or study partner at the end of each minute and entered in the daily log. If a participant cannot complete the exercises as planned, the physiotherapist will provide options ahead of time to modify the exercises to enable the participant to be successful and reach the desired intensity; for example, modifying the height of a stepping block.

Table 1. Tailoring of intervention in collaboration with each dyad (participant and study partner).

Intervention parameters	Tailoring options
Numbers of sessions	20 sessions, 5 days per week, for 4 weeks
Length of each exercise session	Options for each participant: (1) 60 minutes maximum and a minimum of 160 repetitions; (2) reaching 160-300 repetitions
Number of exercises	Tailored for each participant: 2 to 4
Goal of exercises	Targeting balance, mobility, and gait components
Exercise options	(1) Sit-to-stand from a chair, stool, couch; (2) step-up, side steps, high knees, squats, short lunges; (3) standing still, feet together, with arm movements; (4) walking between parallel lines 14-inches apart, walking forward placing foot on lines, walking sideways

Technology

Participants will be provided with a computer for the duration of the study to have access to the remote supervision. The Ontario Telemedicine Network will allow for secure and confidential remote supervision to be completed via videoconference. This platform adheres to all personal health information policies. A link will be emailed to the participant before each session, and a one-click process will facilitate access to the remote supervision. Audio and video will be recorded using screen capture software (Bandicam software), eliminating the use of cloud-based storage.

An individual activity tracking device dashboard will be set up for each participant on the computer. The activity tracking device information collected daily will be synchronized, and the research team will be able to access the dashboard remotely.

Feasibility Measures

Measures of feasibility will be recorded throughout the study. As per Thabane et al [34], four different feasibility factors will be measured: (1) process (adherence rate, retention rate, recruitment rate), (2) resources (length of the intervention, equipment, capacity of transportation for assessments), (3) management (data management), and (4) scientific aspects (safety, dose; Table 2).

Outcomes Measures

Daily repeated measures, pre-post intervention measures, and 1-month follow-up measures will be recorded (Table 3).

Table 2. Measures of feasibility.

Feasibility factors	Measurements
Process	
Adherence rate	Number sessions completed
Retention	Number of participants recruited, number of participants completing study
Recruitment	Severity, transportation issues, availability of study partner, time
Resources	
Length of intervention	Minutes of interventions
Equipment	Reported issues, cost
Transportation capacity	For five face-to-face visits
Management	
Data management	Time spent on data collection and analysis, therapist time on remote supervision
Scientific	
Safety	Adverse events
Dose	Number of repetitions, number of sessions

Table 3. Outcome measures and data collection protocol.

Outcome measures	Baseline	Daily remote supervision[a]		Weekly remote supervision[a]			1-month follow-up
		During exercise program	Posttest	Pretest	During exercise program	Posttest	
Feasibility							
Adherence	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x
Retention	x						x
Recruitment	x						
Equipment	x	x	x	x	x	x	x
Transportation	x		x	x		x	x
Length of intervention		x			x		
Data management	x	x	x	x	x	x	x
Dosage		x			x		
Repeated measures							
Step count	x	x	x	x	x	x	x
Five Times Sit-to-Stand test	x	x[b]	x	x	x[b]	x	x
Pre-post measures							
Quiet stance (two conditions)	x		x	x		x	x
Community Balance & Mobility Scale	x		x	x		x	x
Pre-post self-reported							
Mayo-Portland Participation Index	x		x	x		x	
Fall Efficacy Scale-International	x		x	x		x	
Satisfaction with Life Scale	x		x	x		x	
IBQ[c] and IBQ-Self	x		x			x	
System Usability Scale			x				

[a]These two interventions will be alternating for participants 1 and 2 and participants 3 and 4.

[b]On Mondays with a therapist.

[c]IBQ: Interpersonal Behavior Questionnaire.

Primary Measures: Daily Repeated Measures

Physical activity will be measured by recording step count with an activity tracking device placed at the ankle throughout the entire study [35]. Step count will be recorded every day between intervention sessions to document the effect of the intervention on the amount of physical activity, and during the activity sessions to monitor the number of stepping repetitions.

Functional mobility will be recorded daily with the completion of the FTSTS test. The FTSTS test measures lower extremity muscle strength and transitional movements [33], which contribute to poor balance when decreased [36]. For both supervision frequencies, the FTSTS test will be assessed by the therapist and study partner remotely on Mondays and by the study partner alone during the remaining weekdays.

Secondary Measures: Pre-Post Intervention Measures

As part of the five in-person visits, pre-post intervention measurements will be collected within 5 days of intervention completion. Standing balance will be measured pre- and postintervention for each intervention using the Balance Tracking System Inc (BTracks) [37]. Participants will be asked to stand as still as possible with their feet hip-width apart on the balance board and hands placed on their hips. Two conditions of quiet stance will be measured—eyes open and eyes closed—for three trials of 30 seconds for each condition [38]. Mean velocity (cm/s), root mean square in the anteroposterior and mediolateral planes, and center of pressure (COP) area (95% confidence interval ellipse) will be computed from the balance data.

Functional balance will be measured with the Community Balance and Mobility Scale (CB&M) [39,40]. This clinical test will be administered by an experienced physiotherapist blinded to the intervention study phase (eg, daily or weekly supervision) for each frequency of remote supervision.

Three self-reported questionnaires will be collected pre- and postintervention for both frequencies of remote supervision: the Mayo-Portland Participation Index (M2PI) [41], the Satisfaction With Life Scale [42], and the Fall Efficacy

Scale-International. The Mayo-Portland Adaptability Inventory-4, which includes the M2PI Participation Index, is increasingly used in TBI research and allows for a comprehensive picture of ability, adjustment, and participation. The M2PI [41] is a participation index in which eight domains assess a person's issues within different situations on a Likert scale ranging from 1 to 4. This index will be completed to capture data on participation and explore the impact that remotely supervised physical interventions can have on these three physical domains.

The Satisfaction With Life Scale [42] will be added as a measure of intervention effectiveness. This scale has been widely used with individuals who have survived a moderate or severe TBI and will provide insight into the impact of the remote supervision interventions on overall life satisfaction [43].

The Fall Efficacy Scale-International will allow for a subjective assessment of the fear of falling pre- and postintervention [44]. Fear of falling influences the ability to perform rehabilitation programs independently [45] and is directly correlated with balance deficits [7]. A cut-off score of greater than 23 can be defined as presenting with a fear of falling [46].

One novel questionnaire will be administered at three points in time—baseline session, postintervention 1, and postintervention 2—to assess the quality of the interaction between the therapist and patient. The Interpersonal Behavior Questionnaire (IBQ) [47,48] will assess the patient's perceptions of their therapist's interpersonal behaviors, and the IBQ-Self will assess the therapists' perceptions of their own interpersonal behaviors toward their patients. Each participant will complete their respective part of the questionnaire. The IBQ will be coded in six different categories: autonomy support, autonomy thwarting, competence support, competence thwarting, relatedness support, and relatedness thwarting [47,48] to determine if the therapist interpersonal behaviors are need supportive or need thwarting.

Finally, the System Usability Scale will be collected at postintervention 1 to identify the usability of the Ontario Telemedicine Network system to assess whether it is a good fit for this population [49].

One-Month Follow-Up Measures

A 1-month follow-up will be scheduled to reassess standing balance, functional mobility, and physical activity. Participants will be contacted and asked to wear the activity tracking device on their ankle for the 3 days before the final face-to-face visit. During the final face-to-face visit, the FTSTS [33] and the CB&M scale assessment [39] will be completed. Postural sway via quiet stance will also be reassessed by completing the same COP measures as in pre-post testing. Finally, step count will be gathered by the dyad over 3 days.

Semistructured Interview

As part of the mixed methods design, interviews will be administered with TBI survivors and their study partners separately either face-to-face or via videoconferencing technology at the end of each intervention period (week 4 and week 12). At the beginning of each interview, a brief introduction, confidentiality statement, and description of the research objective will be given to the survivor or the study partner. Each 60-minute, independently completed interview will take place in a private, neutral location [50]. An interview guide will facilitate the probing of topics related to the participant's overall experience, physical activity, safety, experience with remote supervision, and adherence. All interviews will be audio-recorded and saved, password-protected, and encrypted for confidentiality. Field notes will be used to describe the participants' behavior, therapist-perceived comfort levels, and nonverbal demeanor, which will help contextualize the interview and situate the experiences within that context.

Data Analysis

Daily repeated measures data will be analyzed following the four-step single-subject design method of analysis, and pre-post measures for each participant will be descriptively analyzed (Table 4).

Table 4. Outcome measures, analysis, and expected changes.

Outcome measures and method of analysis	Expected changes
Step count	
SSD[a] traditional methods	Increase in step count number
Five Times Sit-to-Stand	
SSD traditional methods	Decrease in time (seconds)
Quiet stance (center of pressure>)	
Descriptive	Velocity: decrease showing an increase in postural stability; root mean square: decrease displacement showing an increase in postural stability; 95% ellipse: decrease displacement showing an increase in postural stability
Community Balance & Mobility Scale	
Descriptive and MDC (7.5)	Increase in total points by a minimum of 7.5
Questionnaires pre-post	
Descriptive	Fall Efficacy Scale-International: decrease number showing decrease concern or fear of falling (score >23 indicates high concern of falling); Mayo-Portland Participation Index: increased index of participation; Satisfaction With Life Scale: increased satisfaction
Questionnaires	
Descriptive	IBQ[b]/IBQ-Self: enhanced communication and self-efficacy between all groups
Feasibility	
Descriptive, feasibility, and process	Adherence: increase in completion of session 80%; retention rate: 100% retention rate; recruitment rate: 80% recruitment rate
Descriptive, feasibility, and resources	Length of the intervention, dose, and intensity by interview; equipment using the System Usability Scale: high score showing usability; capacity of transportation for assessments
Descriptive, feasibility, and management	Data management by therapist field note
Descriptive, feasibility, and scientific aspects	Safety by adverse events: decrease in adverse events

[a]SSD: single-subject design.

[b]IBQ: Interpersonal Behavior Questionnaire.

Analysis for Daily Repeated Measures (Step Count and FTSTS)

In step 1, a visual analysis will be completed by analyzing the trend and identifying stability [51]. A visual comparison of the direction and rate of change as well as variability between all phases (baseline, intervention 1, postintervention 1, washout period, intervention 2, and postintervention 2) [51,52] will be completed.

In step 2, serial dependency will be calculated on all raw data using the lag-1 autocorrelation (r) [46]. The baseline phase for all participants will be more than 5 points; therefore, serial dependency will be assessed on baseline data only [53]. In the case of a statistically significant presence of serial dependency confirmed by the Bartlett test, a first-difference transformation will be calculated before visual and statistical analysis. Once serial dependency is eliminated, a single line graph will be constructed for each participant and daily outcome measure [52].

In step 3, the overall changes between baseline and the first intervention phase and the washout phase and the second intervention phase will be analyzed with the two-standard deviation band method [53,54].

In step 4, an effect size analysis will be completed to supplement visual analysis. The effect size will be calculated by the standardized mean difference of all points proposed by Gage and Lewis [55] and Olive and Smith [56].

Analysis for Pre-Post Measures

All feasibility measures, CB&M scale, COP measures, and self-reported questionnaires will be analyzed descriptively. Mean and standard deviation will allow for the interpretation of intervention effects on outcome measures (Table 3). Clinical significance will also be considered using the CB&M scale, which is 7.5 points for minimal detectable change [39].

To quantify feasibility, a priori cut-offs were defined based on a similar study [57]. The process factors will be quantified as feasible if 80% of the sessions are completed and 100% retention is achieved; dosage factor will be feasible if 80% of sessions achieve 160 to 300 repetitions.

Analysis of Semistructured Interview

A thematic analysis will be used to organize the data [58]. All semistructured interviews will be fully transcribed to text by the main researcher to allow familiarization with the data. Field notes and audio transcription of each interview will be amalgamated, and the main researcher will become deeply involved with the data before disassembling it into codes. A

preestablished framework, the theoretical domain framework [59], will be used to facilitate coding of themes into domains often used in behavioral change and implementation research [52]. If the theoretical domain framework is not suitable for all codes, modifications will be made. As such, general thematic codes will be identified for each transcript and will be collated into a matrix. The matrix will provide a visual representation of all the data to facilitate interpretation. This matrix will be reviewed by a second reviewer, and then interpreted in relation to each question. Patterns between the different participants, within their dyad and between interview one and two, will then be analyzed. This deductive-inductive analysis will provide evidence-based information which could enable a deeper comprehension of the lived experience of remotely supervised home-based interventions.

Ethics

Ethics approval was obtained after a full review process by the Bruyère Research Institute in January 2019, followed by the University of Ottawa board of ethics in March 2019. As per ethics approval, a four-step process will be followed for recruitment and consenting of each participant and caregiver (dyad): recruitment sites will be contacted and recruitment material (poster and video) will be provided, a verbal consent before screening potential participants will be completed on initial contact with primary investigator (J O'Neil, a physiotherapist and PhD candidate), screening of potential participants will be conducted by the primary investigator, and for eligible participants, consent forms will be signed and participants will be given a code to secure confidentiality.

Results

Recruitment is currently underway. Community physiotherapy clinics, military-associated health care professionals, and brain injury associations have received a recruitment site letter, poster, and video. This study is expected to be completed by December 2020.

Discussion

The proposed intervention is complex because of the involvement of multiple technology sources and the inclusion of a complex dyad. Furthermore, the community setting will add another dimension of complexity. However, this type of research is timely because alternative methods of physical intervention delivery are needed to facilitate gains in balance, mobility, and physical activity. Patients who are discharged home and entering the chronic phase of their rehabilitation could benefit from completing an intensive home-based exercise intervention delivered remotely to improve their overall independence. A better understanding of remote supervision and its implementation will allow us to inform future studies around the same constructs.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Example of included exercises in tailored home-based program.
[PDF File (Adobe PDF File)157 KB - resprot_v8i9e14867_app1.pdf]

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Abbreviations

CB&M: Community Balance and Mobility Scale
COP: center of pressure
FTSTS: Five Times Sit-to-Stand
IBQ: Interpersonal Behavior Questionnaire
TBI: traumatic brain injury

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Protocol

Spinal Cord Injury Veterans' Disability Benefits, Outcomes, and Health Care Utilization Patterns: Protocol for a Qualitative Study

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Abstract

Background: An estimated 42,000 people currently living with chronic spinal cord injury (SCI) are veterans. SCI was a common combat-related injury in the World Wars and Vietnam era and now affects more than 11% of military personnel injured in Operation Iraqi Freedom and Operation Enduring Freedom. The Veterans Benefits Administration primarily offers financial compensation for disabilities sustained or re-aggravated during military service, called service-connected disability compensation. With the overwhelming cost of living with an SCI, this monthly financial compensation can provide service-connected veterans and their families with access to additional supportive resources (eg, assistive devices and personal aide) and maintain their quality of life (QOL). Little is known about personal, health, functional, and QOL outcomes associated with service-connected and nonservice-connected status for veterans living with an SCI.

Objective: The aim of this study is to compare the ways in which Veterans Affairs' (VA) service-connected and nonservice-connected status may be associated with health and functional outcomes, choice of health care provider, and overall QOL for veterans living with an SCI and their caregivers.

Methods: This cross-sectional qualitative study will gather data using retrospective chart reviews, semistructured interviews, and focus groups. After obtaining institutional review board (IRB) approval, purposeful sampling techniques will be used to recruit and enroll the following key stakeholders: veterans living with an SCI, family caregivers, and SCI health care providers. Concurrent data collection will take place at 2 sites: Veterans Administration New Jersey Healthcare System and Northern New Jersey Spinal Cord Injury System.

Results: This study was funded in July 2015. IRB approval was obtained by November 2016 at both sites. Enrollment and data collection for phase 1 to phase 4 are complete. A total of 69 veterans, 18 caregivers, and 19 SCI clinicians enrolled in the study. Data analyses for these phases are underway. In phase 5, the follow-up focus group activities are scheduled. The final results are expected by the end of 2019.

Conclusions: The factors that contribute to veterans living with SCI seeking and not seeking VA disability compensation benefits are not well understood in rehabilitation research. Triangulation of these data sources will allow us to compare, contrast, and integrate the results, which can be used to develop clinical guidelines, caregiver training, and patient education programs.

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KEYWORDS

veterans; spinal cord injuries; health care

Introduction

Overview

Spinal cord injury (SCI) is among the most devastating and disabling medical conditions affecting wounded members of the military [1-3]. The Department of Veteran Affairs (VA) is the single largest SCI comprehensive health care provider in the nation [4]. There are approximately 42,000 veterans with SCI eligible to receive care at the VA health care facilities [4]. There is also an unknown number of veterans who sustained an SCI following military service that have never used the VA but are eligible to receive health care from the VA. In addition, a portion of these veterans may be entitled to VA disability compensation and ancillary benefits. Veterans Benefits Administration (VBA) disability compensation benefits are designed to provide financial compensation for disabilities sustained or exacerbated during military service as well as secondary disabilities, which are later causally connected to disabilities that incurred during military service; functional deficits that are incurred or aggravated by military service are adjudicated by the VBA as *service-connected* [5,6]. For example, upon leaving the military, a veteran with a lower back injury applies for, and is adjudicated by VBA as having, a service-connected lower back injury. Later in life, the veteran's spinal cord develops a syringomyelia at the initial level of injury causing a SCI and further functional deficits, which can be adjudicated by VBA as a service-connected disability as well.

As the cost of living with an SCI can be insurmountable, the monthly financial compensation provided to service-connected veterans living with SCI through the VBA can be used to offset the loss of wages. In addition, veterans who are service connected specifically for their spinal cord condition (ie, loss of use feet or hands) may also qualify for additional grants funded through the VBA. These grants promote functional independence by providing resources for the aid and attendance required to maintain the veteran in the least restrictive setting; for example, a VA automobile allowance or specially adapted housing grant where the goal is to help veterans participate in their home life, employment, and social activities that might otherwise be inaccessible and maintain positive quality of life [7,8-10].

Despite VA's efforts to reduce the financial burden associated with successful rehabilitation, independent living, and community integration through disability benefits, a portion of veterans living with SCI have nonservice-connected disabilities because their disabilities were not incurred or aggravated by their military service [5,6]. On the basis of our literature review, there are no studies to date that have compared the impact of having additional financial resources provided to service-connected veterans living with SCI with nonservice-connected SCI-veterans who do not have these additional financial resources. This is a notable oversight because the views and experiences of the service-connected and nonservice-connected veterans living with SCI may be an invaluable source of insight to the VBA disability compensation program's effectiveness beyond the mere provision of additional financial resources. Using a community-based participatory design, the proposed study intends to address this gap using qualitative research methods to compare the impact of service-connected status on veterans' health status, functional outcomes, QOL, family and household, and choice of rehabilitation or medical facilities (ie, VA center or non-VA).

Background

The Department of Veterans Affairs (VA) estimates approximately 450 newly injured veterans and active-duty members receive rehabilitation at VA's SCI centers annually [4]. Results from an analysis of the Joint Theater Trauma Registry found the most common combat-related cause of spinal injuries during the Global War on Terrorism are explosions, which account for more than half of the cases, followed by motor vehicle accidents and gunshot wounds [1,11,12].Reports based on data from the National Spinal Cord Injury Database (NSCID) estimate that the average lifetime costs for a 25-year-old individual with high tetraplegia to be more than 3 million dollars, excluding additional opportunity costs such as lost wages, benefits, and productivity [13]. A disproportionate number of individuals living with SCI (62.7%) reside in households with an annual income of US $25,000 or less, and the NSCID reports that only 11.5% of persons with SCI report being employed 11-year after injury [14]. The evidence that socioeconomic disadvantage is common among persons with SCI suggests that this group is at increased risk for poorer health and functional outcomes, given the pervasive negative relationship between socioeconomic disadvantage and health and functional status [15]. Furthermore, these indicators of disadvantage may be exacerbated by the complexity of military service among veterans living with SCI, such as comorbid traumatic brain injury, pain, and posttraumatic stress disorder (PTSD) [16], suggesting that an examination of the provision of financial resources for veterans living with SCI to support health outcomes, functional independence, and QOL is warranted.

The primary goal of VA SCI and Disorders (SCI/D) services is to restore functioning, reduce secondary complications, and promote the health and sustainability of functional independence to maximize QOL after injury [17]. The VA SCI/D System of Care is referred to as a *hub and spoke* system. The VA SCI/D System of Care includes 25 regional SCI/D Centers (known as *hubs*) that provide comprehensive range of care including, inpatient and outpatient rehabilitation, specialty care, and coordinated lifelong continuum of care delivered by interdisciplinary teams [17]. After rehabilitation, most veterans living with SCI return to live in the community [17]. Thus, independent living, community reintegration (eg, functional independence, social participation, and employment access), and QOL are top priorities for VA SCI center rehabilitation [14,17].

The SCI Model Systems (SCIMS) are specialized programs of care in SCI that gather information and conduct research with the goal of improving long-term functional, vocational, cognitive, and QOL outcomes for individuals with SCI. SCIMS, sponsored by the National Institute on Disability, Independent Living, and Rehabilitation Research, Administration for Community Living, US Department of Health and Human

Services, supports innovative projects and research in the delivery; demonstration; and evaluation of medical, rehabilitation, vocational, and other services to meet the needs of individuals with SCI. The Northern New Jersey Spinal Cord Injury System (NNJSCIS) was established as a SCIMS in 1990. The NNJSCIS provides a comprehensive continuum of state-of-the-art care for persons with spinal cord injury and their families from the time of injury through rehabilitation and return to the community.

Veterans Disability Compensation Benefits

VA provides monthly disability compensation benefits to veterans who develop medical conditions and disabilities related to military service; that is, who are deemed *service connected* [5,6,18-19,20]. Veterans seek service connected disability compensation benefits when: (1) they are discharged from the military because of a disability that was incurred or aggravated during military service; (2) a disability manifests itself after the veteran leaves the military but the veteran believes he can prove that its origins occurred in the military (ie, low back pain because the veteran was an infantryman who carried a heavy ruck sack on multiple deployments); (3) a veteran has an earlier service connected disability that results in a worsened disability (eg, service connected knee injury leads to a fall resulting in a SCI); or (4) a veteran is diagnosed with a condition that is presumptively considered service-connected (ie, if a veteran is diagnosed with amyotrophic lateral sclerosis [21] following their military service, it is presumptively considered service-connected and compensable). To qualify for disability compensation benefits, veterans have to submit an disability compensation application and complete a medical assessment to ascertain the functional impact of their disabilities and its impact on a veterans' *average impairment in earning capacity* [5,6,22-23,18-19]. On the basis of the VBA Schedule for Rating Disabilities, disability ratings range from 0% to 100% in 10% increments (ie, *scheduler ratings*), with a higher percentage of rating equaling a greater functional impairment and amount of disability compensation awarded. Typically, a VA disability rating is derived from an algorithm that combines the individual scheduler ratings of each compensated disability [5,6]. Therefore, two 10% disability ratings do not equal 20%. The algorithm takes into account the number and severity of each scheduler rating and attempts to calculate the overall impact on average earning capacity. Typically, veterans with service-connected SCIs that impact their ability to walk and cause neurogenic bowel and bladder have scheduler ratings of 100% for bilateral loss of use of lower extremities, 60% for neurogenic bladder, and 60% for neurogenic bowel [5,6]. The algorithm combines these ratings to 100% and awards maximum VA disability compensation benefits [5,6]. Unlike Social Security Disability Insurance, which by definition can only be awarded when a disability results in the inability "to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months," VA disability compensation benefits are tax-exempt and not automatically discontinued if the veteran returns to work [5,6,22-23,18-19].

Research Problem

Little is known about the differential impact of service-connected status on the health status, functional outcomes, QOL, and health care utilization patterns of veterans living with SCI. Interestingly, veterans service-connected for PTSD have been found to report high rates of medical impairment, psychiatric symptomatology, and utilization of medical and mental health services [22,23,18]. Furthermore, veterans with PTSD sought service-connected disability compensation of internal factors (eg, tangible needs, need for the problem identification and clarification, and justification and legitimization of *invisible wounds*) and external factors (eg, encouragement from trusted others and professional assistance associated with seeking disability benefits) [19]. These findings suggest there may be a range of factors to consider that may differentially impact veterans living with an SCI based on their service-connected status.

The proposed study intends to address this gap in the literature using qualitative research methods to explore the perspectives of service-connected and nonservice-connected veterans living with SCI, family caregivers as well as SCI clinicians about factors that contribute to these veterans' health status, functional outcomes, and health care utilization. On the basis of the aforementioned literature, individual/personal factors, socioeconomic, family, and health system factors will be explored. Individual factors such as demographic characteristics (eg, age), cultural beliefs, socioeconomic status (eg, education and income), and health risk behaviors (eg, smoking and alcohol use) have been found to the impact on health status, functional outcomes, and health care utilization in veterans living with SCI [24]. Family caregivers provide assistance that is critical to sustaining health status, functional gains, and access to health care services as Veterans living with SCI return to the community and will provide information about household/community barriers observed across service-connected and nonservice-connected veterans living with SCI [25-27]. SCI health care providers, such as physicians, nurses, social workers, and occupational and physical therapists will provide insights into clinical factors that could contribute to health status, functional outcomes, and health care utilization among veterans living with SCI. Given the high cost of living with an SCI, understanding veterans' reasons for seeking or not seeking service-connected disability compensation benefits will provide insights about the ways in which veterans' manage their health, functioning, health care, and QOL.

Conceptual Model

This investigation will be guided by the framework of the International Classification of Functioning, Disability, and Health (ICF) [25,26] to examine how service-connection status influences health, function, and health care utilization patterns among veterans living with an SCI. The ICF model conceptualizes disability as an interaction between impairment, functioning, personal factors, and the environment. The ICF can be used to identify, mitigate, or remove societal barriers to full participation of persons with SCI [27-29]. Functioning and disability are viewed as a complex interaction between the impairment of individual, environmental (ie, contextual), and

personal factors. Within this framework, SCI is a condition that most often results in impairments such as permanent paralysis. Paralysis then leads to secondary complications, functional limitations, and restrictions to community participation over time. The ICF model serves as a rehabilitation model that will be used to guide the data collection, measuring project outcomes, and designing of clinical guidelines, family interventions, caregiver training, and patient education programs (Figure 1).

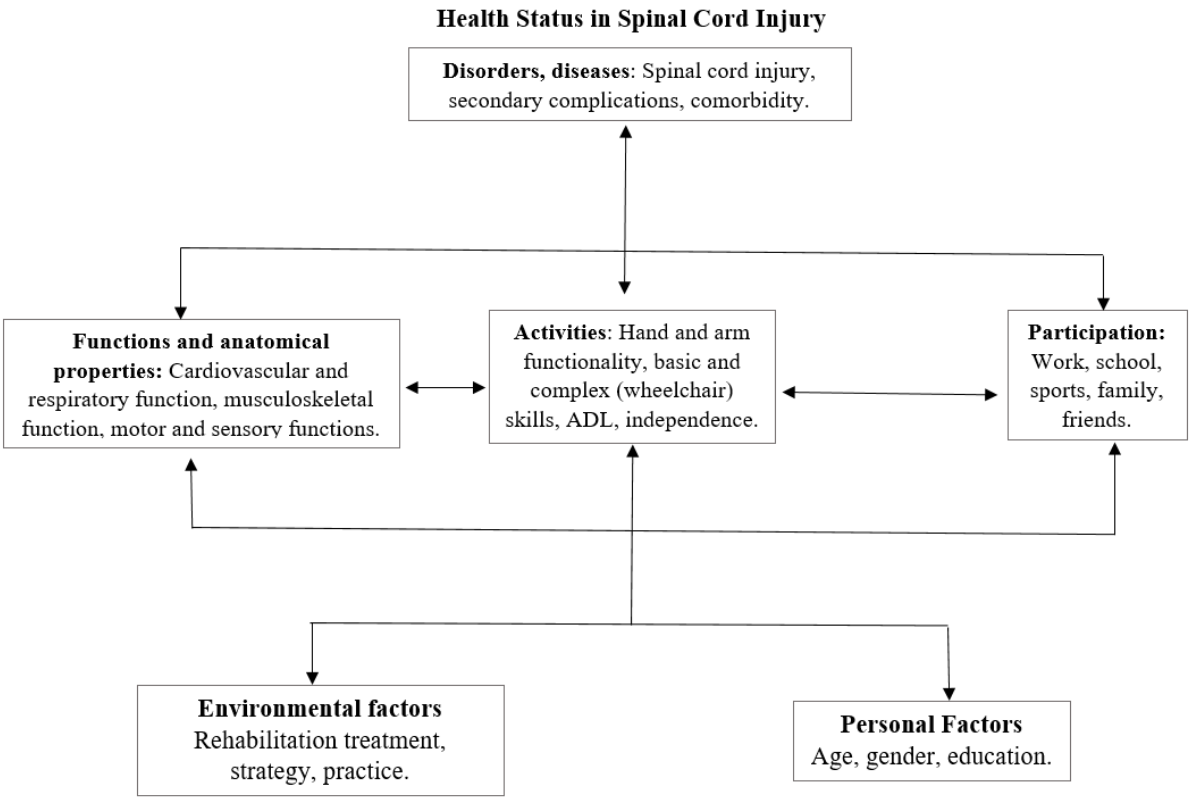
Specific Aims

The proposed project will use qualitative methods to examine the factors associated with outcomes for service-connected and nonservice-connected SCI. Qualitative methods have the advantage of allowing us to address these aims in a manner that is meaningful to individuals who are actively involved in SCI veteran rehabilitation: veterans living with SCI, family caregivers, and SCI clinicians. We propose the following aims:

1. To describe veterans living with SCIs' reasons for seeking versus not seeking service-connected disability compensation and the factors that influence their choice.
2. To explore the impact of service-connected disability compensation on health status, functional outcomes, QOL, and medical decision making (eg, choice of VA SCI Center versus private sector).
3. To explore the impact of service-connected disability compensation on the family caregivers and households of veterans living with SCI.
4. To explore SCI clinicians' perspectives on the impact of service-connected disability compensation status on the provision of adequate long-term health care and rehabilitation for veterans living with SCI.
5. To develop a set of practice and policy recommendations about the impact of service-connection status of veterans living with SCI on clinical and policy guidelines, family interventions, caregiver training, and patient education programs.

The proposed work is significant because it will provide new knowledge about veterans living with SCI with and without service connected disability compensation in the realm of family caregiver support, access to community resources, personal factors, and health behaviors, including patient-provider relationships and their impact on health status, functional outcomes, and QOL. The findings will describe areas of care considered priorities for veterans living with SCI and families that must be clearly integrated into clinical care to support the successful maintenance of health status, functional outcomes, and QOL.

Figure 1. International Classification of Functioning model for spinal cord injury (adapted from de Groot et al, 2009 [27]). ADL: activities of daily living; ICF: International Classification of Functioning, Disability and Health; SCI: spinal cord injury.



Methods

The study protocol, research team and data collection instruments were reviewed and approved by the institutional review board (IRB) at each study site as well as US Army Medical Research and Materiel Command`s Office of Research Protections, Human Research Protection Office.

Research Design

This cross-sectional qualitative study will use a community-based participatory approach to examine the reasons for seeking disability compensation benefits, factors associated with outcomes, and choice of health care facility among veterans living with SCI with and without service-connected disability benefits. Community-Based Participatory Research represents a collaborative process between researchers and community partners; builds on the unique strengths, knowledge, and resources within a given community by employing local knowledge in the understanding of health problems and their potential solutions; and facilitates collaboration throughout all phases of the research [30].We will collaborate and gather data from veterans living with SCI, caregivers, and SCI professionals who will serve as *experts* to explore the health status, functional outcomes, and QOL of veterans living with SCI with different types of disability benefits and who decide to receive their health care from VA centers and non-VA.

Interdisciplinary Project Team

To achieve these aims, we assembled a highly productive and interdisciplinary team of SCI/D researchers and community advisors with expertise in qualitative research methods, VA SCI *hub and spoke* system of care, private care sector of SCI care, caregiving, and SCI research.

Participants

The study will collect data from 3 groups of participants involved in sustaining the health status, functional independence, and QOL of veterans living with SCI who are impacted by the type of disability benefits and health care utilization patterns:

Spinal Cord Veterans

An equal number of veterans living with SCI receiving clinical services or who have previously participated in research at the East Orange Campus of the VA New Jersey Health Care System (VANJHCS) or Northern New Jersey SCI Model System (comprised the Kessler Foundation and Kessler Institute for Rehabilitation) will participate in phase 1 (n=15 per site) and 2 (n=30 per site) of the study (described below).

Inclusion Criteria

Inclusion criteria are being male, veterans (or served on active duty service in the US Armed Forces), at least 18 years of age, SCI that occurred at least 1 year ago, and receiving health care/rehabilitation at the participating VANJHCS and/or a participating Spinal Cord Injury Model System site or Spinal Cord Injury Model System (SCIMS).

Exclusion Criteria

Exclusion criteria are inability to communicate because of neurological impairment (eg, dementia or aphasia); identifying as a female. We limited the scope of the study to patients to male veterans living with SCI because there are not likely to be sufficient numbers of female veterans living with SCI to be able to recruit a meaningful sample of them, given a larger proportion of people with SCI and veterans are males and thus beyond the scope of this project.

Spinal Cord Injury Veteran Family Caregivers

SCI often results in physical limitations such that receiving assistance from others is critical to maintaining health and facilitating full societal integration. The help received ranges from assistance with basic daily activities such as bowel and bladder management and dressing, as well as instrumental activities of daily living, including managing household finances, shopping, or transportation. In the United States, most home care is provided through informal mechanisms by family members [31], and almost 70% of people with SCI receive some form of assistance and support from family members [32]. One individual in a family frequently assumes most or all the responsibilities of caring for a person with a disability [33], and this responsibility can carry with it several physical, emotional, social, and economic risks. We will recruit a sample of 10 SCI veteran family caregivers from each site who have provided care on a daily basis, for at least 6 months, to SCI, and preferably, these family members identify as the *primary* caregivers. Family caregivers who may be eligible to participate in the focus groups or interviews will be identified by clinical staff (social workers, therapists, and others) or an SCI veteran who participated in a semistructured interview. A member of the research team will contact the family caregiver to inform them about the study and determine if they meet the eligibility criteria to provide additional information and make arrangements to obtain informed consent before the start of focus group or interview data collection.

Spinal Cord Injury Veteran Clinicians

Clinicians' perceptions are important because they may affect patient-provider relationships, the course, and the outcome of treatment. Clinicians have knowledge of the medical and functional consequences of SCI and experience providing training to veterans living with SCI and their family caregivers to plan for adjusting to home life and community reintegration. SCI clinicians at each participating center will be informed of the study through written (flyers and emails) and oral communications with local study leaders and/or supervisory staff. We will recruit a sample of 10 clinicians at both sites that includes staff members who have experience providing direct care or services to veterans living with SCI at each of the research sites. The SCI clinical staff will include physiatrists, nurses, social workers, physical, recreation, and occupational therapists who have at least 2 years of experience providing care to SCI. Clinicians who are interested in participating and wish to be contacted by the research team will receive additional information and, if interested, give informed consent before the start of focus group data collection.

Each group of participants has real-world experiences and clinical knowledge that will inform the content of the key practice recommendations that can be readily integrated into

clinical guidelines, family interventions, caregiver training, and patient education programs.

Study Sites

Two study sites that serve veterans living with SCI in New Jersey will conduct the proposed study: VANJHCS and Northern New Jersey Spinal Cord Injury System. A description of each research site is provided in Multimedia Appendix 1: facilities, existing equipment, and other resources. These sites were selected for their access to diverse communities of veterans living with SCI served by the respective research institutions. Each site has an average of 190 to 429 veterans living with SCI in their respective patient registries.

Sampling Strategy and Recruitment

After obtaining approval from the IRB at the study sites, purposeful sampling strategies will be used to identify and recruit potential study participants. A research coordinator (RC) will recruit potential participants using advertisements, brochures, and referrals from SCI registries at each collaborative site. If we do not get an adequate recruitment response, we will implement the snowball recruitment technique that involves asking participants to inform and encourage friends, colleagues, and other peers to participate [34].

In recent years, data saturation has become the gold standard by which purposive sample sizes are determined in qualitative research [35]. Theoretical saturation is achieved when focus groups or interviews do not generate novel ideas. The sample sizes proposed for each study phase described below are based on minimum sample size recommendations for common qualitative study designs [36]. Furthermore, our sampling strategy will be flexible, evolving as the study progresses through the 4 phases, until the point of redundancy in emerging themes is reached to meet the purposes of the study.

Once each participant completes oral and written informed consent and is scheduled for interview or focus group session, he/she will receive a telephone reminder 2 weeks before the interview or focus group as well as a written letter 1 week beforehand. The day before the event, the consultant will make 1 last round of confirmatory phone calls. Participants will be compensated for their time. In addition, to maintain enrollment and participation, we will provide transportation cost for a portion of veterans living with SCI and family caregiver on an as-needed basis.

Data Collection

Three methods of qualitative data will be collected: chart review, semistructured interviews, and focus groups. These 3 qualitative data collection methods will be implemented over 4 phases of sequential qualitative data collection outlined in Table 1. The content of the chart reviews, interviews, and focus groups will be stratified based on disability benefits. The structure and content of questions will be modified based on joint planning with the community advisory board (CAB) during the course of the project. Of particular interest is how these groups *independently* interpret the reasons and impact of the disability benefits on veterans living with SCIs' . Results from each phase will be analyzed separately and then merged to inform the content of the subsequent phases as well as the set of practice recommendations that can be readily integrated into clinical guidelines and family interventions. Multimedia Appendix 2 provides detailed description of sample items from the data collection instruments.

Table 1. Research plan.

Phase	Data collection	Purpose	Data source
I	Chart review	Prepare and supplement data gathered in subsequent phases	Medical records
II	Semistructured interviews	Exploring SCI[a] veterans' understanding and perceptions of VA[b] disability compensation benefits	SCI
III	interviews/focus groups	Identify SCI family caregivers' perspectives about the impact of disability benefits on the household	SCI family
IV	Focus groups	SCI clinicians' perspectives of the impact of VA disability benefits on SCI and provision of adequate long-term health care and rehabilitation	SCI
V	Focus groups	Develop key elements for clinical practice recommendations	Triangulation of study findings, feedback from service

[a]SCI: spinal cord injury.

[b]VA: US Department of Veterans Affairs.

Phase I: Chart Review

The RC will be trained to use a standardized chart abstraction instrument to gather demographic, clinical, and disability benefits data. The chart review will be designed to help prepare and supplement data gathered in subsequent phases by providing data that will (1) inform the development of discussion questions for the participant interviews and focus groups; (2) confirm the veterans living with SCI disability status and rating; and (3) documentation of health status, functional information, and patient/family education logs gathered during the most recent annual evaluation of 30 veterans living with SCI (15 per site). An annual evaluation was defined as a *comprehensive annual history/physical exam with specialty assessments*, offering an annual evaluation is mandated for patients with SCI in the Veterans Health Administration (VHA) [17].

Phase II: Semistructured Interviews

Semistructured interviews will be aimed at capturing service-connected and nonservice-connected veterans living

with SCI perspectives on ways in which their financial compensation (or lack thereof) impacts their health status, functional independence during community reintegration, QOL, and their utilization of health care. The sample will be equally split between study sites (n=30) veterans. We will modify items from the benefits coverage inventory, a measure that has been used in previous research to assess rehabilitation/independent living benefits received after discharge in 5 areas: housing, personal care assistant, transportation; outpatient therapies (eg, physical therapy, occupational therapy, and vocational rehabilitation), and equipment (durable and nondurable). The measure asks about who pays for these items (self, insurance, or other). We will work with the CAB to develop semistructured interview questions that relate to service-connected disability benefits. The semistructured interview will discuss veterans living with SCIs' likes and dislikes of the being service-connected or nonservice-connected—their perceptions about whether disability benefits may be viewed as a barrier to independence, and difficulties with bureaucracy for some veterans living with SCI. The interview will ask veterans living with SCI to express their experiences about unexpected barriers associated with seeking service-connected financial compensation. Key questions will focus on their health status, maintenance of their functional independence during community reintegration, health care, and rehabilitation experiences. The individual semistructured interview allows for rapport and confidence building at a sensitive time after injury so that more honest opinions and attitudes may be revealed more readily than in a group setting. The interviewer can answer respondent questions, probe for additional answers, and observe visual cues. To facilitate access to veterans living with SCI who are unable to come to the research site for an interview, we will use the VA's real-time video health tool—Clinical Video Telehealth that is a technology that is frequently used in the VA to promote video communication between patients and providers (see Multimedia Appendix 3—Facilities, Existing Equipment, and Other Resources). To ensure quality data assurance, interviews will be audiotaped and transcribed. After the interview is completed, the RC and research assistant will summarize their notes and review the results with the principal investigator (PI). Spot checks of the transcripts comparing them with the audiotapes will be done to ensure accuracy of the transcripts.

Phase III: Spinal Cord Injury Veteran Family Caregivers

SCI family caregivers provide assistance that is critical to sustaining health status, functional gains, and access to health care services as veterans living with SCI return to the community and will provide information about household/community barriers observed across service-connected and nonservice-connected veterans living with SCI. We give family caregivers the option to participate in a caregiver focus groups or individual semistructured interviews. The qualitative data collection methods will be used to ascertain SCI veteran family caregivers' perspectives on the impact of disability benefits on their family life, including household finances, the health of SCI veteran as well as their own health, and the provision of health care/rehabilitation to sustain the functional independence of the SCI. Caregivers will also be asked to provide suggestions about potential solutions to the problems they identify to facilitate their efforts providing care to an SCI veteran that is service connected or not service connected.

Focus groups are an efficient way to collect data from several people simultaneously, and they explicitly use group interaction as part of the method [34]. Focus groups will allow us to elucidate the shared experience and challenges of seeking disability benefits and the factors associated with outcomes and choice of health care facility among veterans living with SCI with and without service-connected disability benefits. This recruitment strategy will account for nonattendance and ensure optimum focus group size and participant comfort [34]. Multimedia Appendix 2 gives a draft of the focus group script.

The RC will take field notes on a structured data recording sheet, based on the focus of group script/interview guide. The field notes will include key points, notable quotes, and important observations such as silent agreement, body language, group mood, and ironic or contradictory statements. Each focus group will be recorded and transcribed, but anonymity will be maintained. The focus groups will be recorded with a password-enabled digital recorder, and we will transfer all the recordings to the secure VA network after each interview is completed. At the end of each focus group, the PI will give a brief oral summary of critical points that the participants can verify, amend, or change. The PI and RC will meet for a debriefing immediately after each session to share their perceptions of first impressions, critical points, and notable quotes and to highlight and contrast findings from earlier focus groups. This debriefing will also include any notable circumstances that influenced the discussion, resolution of questions, and potential modifications for subsequent groups and/or interviews.

Phase IV: Spinal Cord Veterans' Clinicians

We will conduct focus groups with SCI clinical staff from the Veterans Administration New Jersey Healthcare System and SCIMS health care systems. The focus groups will be conducted with approximately 10 interdisplinary SCI clinicians per group to provide insights into the following: (1) clinical factors of veterans living with SCI who seek different types of disability compensation benefits (ie, service connected and others are nonservice connected); (2) describe their perception about the relationship between disability benefits and health status, functional outcomes and health care utilization among veterans living with SCI; (3) identify VA and private-sector health care system issues related to disability compensation benefits, which are obstacles for veterans living with an SCI; and (4) identify solutions to address these concerns.

Phase V: Developing Practice and Policy Recommendations

Qualitative Data Analysis Plan

To design a useful set of practice recommendations, we will analyze results from phases I to IV separately and then merge them to prepare the content materials for phase V. The chart review, interview, and focus group data will be prepared for analysis by converting the raw data (eg, field notes) into partially processed data (eg, write-ups and transcripts), which will then

be coded and subjected to an analytic theme. The analysis will focus on the key research questions and include the following steps:

1. Read each transcript in an editing style to augment an initial codebook template developed from the ICF guidelines and interview guide.
2. Read and reread highlighted portions to develop keywords (themes, patterns, or categories).
3. Divide the themes, patterns, and categories into groups by the research questions.
4. Examine the convergence/divergence by completing the following steps:

Convergence will be examined by determining what themes fit together to develop the internal homogeneity and external heterogeneity.

Internal homogeneity will be determined by analyzing the themes to see which are more similar, and external heterogeneity was determined by analyzing the themes to see which ones are distinctly different from each other [37].

These processes will enhance the credibility of the research. Divergence will reveal some of the patterns within the categories and helps to make connections among the themes for categorical saturation [37].

Qualitative data collected in phases I to IV will generate its own findings to add additional information to our understanding about the reasons veterans living with SCI seek different types of disability benefits and how these factors that are associated with health status, functional outcomes, and QOL. Triangulation is methodological approach that contributes to the validity and reliability of qualitative data collection when multiple method and sources are employed [38]. Triangulation will allow us to compare, contrast, and integrate the results from the chart reviews, veterans living with SCI, family caregivers, and SCI clinicians. Triangulation from the focus group and interview data will also allow us to ensure results are being confirmed across data sources and identify what is being uniquely provided by different data sources. Investigator triangulation, which consists of multiple—rather than single—observers, will be used to strengthen the validity and credibility of the qualitative findings observed in each phase of the study [38]. A very large amount of raw data will be generated; therefore, narrative data will be stored and analyzed using QSR International's NVivo 12 software. This type of software facilitates thematic coding, interrater reliability, and correlation of themes with demographic characteristics. NVivo can also be used with Excel spreadsheets to generate matrices that demonstrate relationships between variables and themes.

Developing Practice and Policy Recommendations

Using the themes generated from the qualitative analyses, we will work with the CAB to summarize to identify the most frequently cited factors (ie, problems and solutions) that impact veterans living with SCIs' decision to seek service-connected disability benefits (ie, those that are mentioned by more than 1 data source) and across samples of participants—a process that is known as *group-to-group validation* [34].

There are a number of steps outlined in the literature used to develop targeted recommendations for clinical guidelines, developing recommendations for patient and family educational resources, and policy-level interventions. First, the research team will generate a summary of the most frequently cited factors identified from the data as recommendations to the CAB. Examples of potential interventions include revisions to existing patient and family education material related to programs and services available from the VA for veterans with SCI; educational interventions for SCI clinicians to make them more aware of resources available from the VA that are correlated with positive clinical practice outcomes for veterans with SCI veteran, and their families, caregivers, and other clinicians; procedures to help clinicians identify veterans living with SCI at civilian hospitals and connecting these veterans and their families with knowledgeable VA advocates (eg, VA SCI social worker or veteran service organization) and VA disability compensation and health care resources.

Second, the CAB and research team will have monthly consensus meetings, which will be used to evaluate aspects of the most frequently cited individual, family, SCI clinician, and systemic factors generated from the data: importance to veterans living with SCI and modifiability. Determination of importance can be obtained in several ways, such as the CAB rating on the degree of importance, and assessing socially significant implications of the qualitative findings. The CAB and research team will collaboratively rate the modifiability of the individual, family, SCI clinician, and systemic factors from the qualitative data by asking the question, "Can this problem easily be addressed?" or "Can this solution be implemented pragmatically?" The collaborative will rate these individual, family, SCI clinician, and systemic factors as (1) factors that can be completely changed, (2) factors that may be modified, but we are unable to change them completely, and (3) factors that are nonmodifiable. Third, the CAB and research team will select *targets of change*. After identifying the factors that are both important and modifiable, the CAB and research team will decide which factors will be targeted for recommendations for interventions. Finally, the CAB and research team will select promising strategies or key recommendations to develop an intervention action-point document. The intervention action-point document will be a road map toward the operationalization of an educational intervention for SCI, families, SCI clinicians, and policy recommendations for the VBA.

Content of the intervention action-point document will be evaluated assessed for their appeal, clarity, and appropriateness for the target users. We will recruit veterans living with SCI and family caregivers who participated in phases I to III. We will recruit approximately 5 veterans living with SCI and 5 family caregivers. Veterans living with SCI and family caregivers will be asked if they are willing to participate in future groups or interviews. Members of the research team will recruit those who agreed using personal phone calls. If we do not get an adequate response from the previously identified participants, advertisements, brochures, word of mouth, and the aforementioned snowball technique will be used. An honorarium

will be offered to compensate participants for their time and transportation.

Results

The project was funded in July 2015, and recruitment was completed in October 2018.

A total of 69 male veterans living with an SCI participated in medical chart review and interview phases of the study. The mean age of the sample was 59.5 years (SD 14.8; range 23-86). Most of the veterans self-identified as non-Hispanic white (61%, 42/69), married (52%, 36/69), had some college education (80%, 55/69), and unemployed (93%, 64/69). In terms of military experience, approximately one-third served in the army (39%, 27/69) and primarily in the Vietnam era (32%, 22/69). The majority of veterans sustained their injury after military service (75%, 52/69), and were living with paraplegia (53%, 37/69) for an average of mean 15.0 years (SD 13.0. Almost two-thirds; 64%, 44/69) of the veterans self-identified as nonservice connected and 36% (25/69) were service connected for SCI or another disability (eg, PTSD). A total of 18 caregivers participated in focus groups and interviews at the 2 sites. All of the caregivers were females, the mean age of caregivers was 64.8 years (SD 10.8) and reported caregiving for their loved one for approximately, 15.9 years (SD 11.4). A total of 9 SCI clinicians participated in a focus group at Veterans Administration New Jersey Healthcare System and 10 at the SCIMS site. Comparable clinical professions (eg, psychiatrist, nurse, and therapists) were represented in each focus group and average of 11.5 years (SD 8.8) working in their current positions.

Preliminary content review of narrative data suggests that veterans living with an SCI and caregiver participants varied in their reasons why they did not apply for VA disability compensation, including a lack of knowledge and misinterpretations about the VA disability compensation eligibility and health care coverage from the VBA and VHA, respectively.

Discussion

This qualitative study will use a community-based approach to derive information from veterans living with SCI, family caregivers, and SCI clinicians about their day-to-day experiences with being service connected or nonservice connected status. Of particular interest is how these groups *independently* interpret the reasons and impact of service-connected compensation (or lack thereof) on the health status, functional outcomes, QOL, and health care utilization of veterans living with SCI. Preliminary findings suggest a small proportion of participants receive VA service-connected disability compensation benefits. Participants' responses indicate that veterans living with an SCI and their caregivers may not be fully aware of their eligibility for VA disability compensation, making it more difficult to make an informed decision about pursuing VA disability compensation benefits. To make an informed decision about eligibility for VA disability compensation benefits, veterans living with SCI should be connected with an experienced veterans benefits advocate (ie veterans service officer). Study findings will be used to generate a set of practice recommendations to the clinical guidelines, family interventions, caregiver training, and patient education programs that can be tested in a future large-scale multisite quantitative study to devise targeted community-based interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Department of Defense, United States of America.
[PDF File (Adobe PDF File)156 KB - resprot_v8i10e14039_app1.pdf]

Multimedia Appendix 2
Data collection instruments.
[PDF File (Adobe PDF File)129 KB - resprot_v8i9e14039_app2.pdf]

Multimedia Appendix 3
Facilities and resources.
[PDF File (Adobe PDF File)201 KB - resprot_v8i9e14039_app3.pdf]

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Abbreviations

CAB: community advisory board
ICF: International Classification of Functioning, Disability, and Health
IRB: institutional review board
NNJSCIS: Northern New Jersey Spinal Cord Injury System
NSCID: National Spinal Cord Injury Database
PI: principal investigator
PTSD: posttraumatic stress disorder
QOL: quality of life
RC: research coordinator
SCI: spinal cord injury
SCIMS: Spinal Cord Injury Model System
VA: Department of Veterans Affairs
VANJHCS: East Orange Campus of the Veterans Affairs New Jersey Health Care System
VA SCI/D: Department of Veterans Affairs Spinal Cord Injury and Disorders
VBA: Veterans Benefits Administration
VHA: Veterans Health Administration

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Protocol

Use of Human-Centered Design to Improve Implementation of Evidence-Based Psychotherapies in Low-Resource Communities: Protocol for Studies Applying a Framework to Assess Usability

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2020/3/e18241/

Abstract

Background: This paper presents the protocol for the National Institute of Mental Health (NIMH)–funded University of Washington's ALACRITY (Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness) Center (UWAC), which uses human-centered design (HCD) methods to improve the implementation of evidence-based psychosocial interventions (EBPIs). We propose that usability—the degree to which interventions and implementation strategies can be used with ease, efficiency, effectiveness, and satisfaction—is a fundamental, yet poorly understood determinant of implementation.

Objective: We present a novel Discover, Design/Build, and Test (DDBT) framework to study usability as an implementation determinant. DDBT will be applied across Center projects to develop scalable and efficient implementation strategies (eg, training tools), modify existing EBPIs to enhance usability, and create usable and nonburdensome decision support tools for quality delivery of EBPIs.

Methods: Stakeholder participants will be implementation practitioners/intermediaries, mental health clinicians, and patients with mental illness in nonspecialty mental health settings in underresourced communities. Three preplanned projects and 12 pilot studies will employ the DDBT model to (1) identify usability challenges in implementing EBPIs in underresourced settings; (2) iteratively design solutions to overcome these challenges; and (3) compare the solution to the original version of the EPBI or implementation strategy on usability, quality of care, and patient-reported outcomes. The final products from the center will be a streamlined modification and redesign model that will improve the usability of EBPIs and implementation strategies (eg, tools to support EBPI education and decision making); a matrix of modification targets (ie, usability issues) that are both common and unique to EBPIs, strategies, settings, and patient populations; and a compilation of redesign strategies and the relative effectiveness of the redesigned solution compared to the original EBPI or strategy.

Results: The UWAC received institutional review board approval for the three separate studies in March 2018 and was funded in May 2018.

Conclusions: The outcomes from this center will inform the implementation of EBPIs by identifying cross-cutting features of EBPIs and implementation strategies that influence the use and acceptability of these interventions, actively involving stakeholder

clinicians and implementation practitioners in the design of the EBPI modification or implementation strategy solution and identifying the impact of HCD-informed modifications and solutions on intervention effectiveness and quality.

Trial Registration: ClinicalTrials.gov NCT03515226 (https://clinicaltrials.gov/ct2/show/NCT03515226), NCT03514394 (https://clinicaltrials.gov/ct2/show/NCT03514394), and NCT03516513 (https://clinicaltrials.gov/ct2/show/NCT03516513).

International Registered Report Identifier (IRRID): DERR1-10.2196/14990

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KEYWORDS

implementation science; human-centered design; evidence-based psychosocial interventions

Introduction

Background

Psychosocial interventions (eg, psychotherapy, counseling, and case management) are a preferred mode of treatment by most people seeking care for mental health problems, particularly among low-income, minority, geriatric, and rural populations [1-7]. Despite numerous studies demonstrating the effectiveness of evidence-based psychosocial interventions (EBPIs), they are rarely available in community service settings [8-10]. A landmark report by the United States' Institute of Medicine [11] noted that EBPI availability is limited by clinicians' abilities to effectively learn and adopt new practices (ie, capacity), intervention complexity, and limited support to sustain quality delivery. EBPI implementation is particularly challenging because most people receive treatment for mental illness in nontraditional or integrated settings such as primary care [12] and schools [13,14]. EBPIs were typically not developed for these settings, resulting in poor contextual fit and low adoption [15,16]. To address EBPI implementation barriers, decades of research has focused on provider, patient, setting, and policy barriers [17], yet actionable and cost-efficient solutions remain elusive [18]. Numerous implementation strategies have been developed to facilitate EBPI delivery [19-21], but the interventions and their accompanying implementation strategies are complex processes that are often difficult to deliver [22,23]. As a result, the science-to-service gap for EBPIs remains significant.

Usability as a Key Implementation Factor

The usability of EBPIs and implementation strategies are a major challenge to successful implementation and one that has largely been largely overlooked by health care researchers who focus on promoting the implementation of evidence-based practices in routine service settings. Usability is defined as the degree to which a program can be used easily, efficiently, and with satisfaction/low user burden by a particular stakeholder [24]. Although the concept of usability has most traditionally been applied to digital products, usability metrics and assessment procedures are much more broadly relevant. Indeed, with regard to EBPIs and implementation strategies, usability has also been identified as a key determinant of implementation outcomes (eg, intervention adoption, service quality, and cost) and clinical outcomes (eg, symptoms and functioning) [25].

Evidence-Based Psychosocial Interventions Usability

EBPIs are complex psychosocial interventions involving interpersonal or informational activities, techniques, or strategies with the aim of reducing symptoms and improving functioning or wellbeing [11]. Usability standards sit in striking contrast to the current state of EBPIs, which are generally difficult to learn, requiring several months of training and supervision [26-28]; impose a high degree of user burden or cognitive load [22]; and do not fit well into typical provider and patient workflows [29]. Most implementation research focuses on creating "hospitable soil" (ie, modifying individual or organizational contexts to fit the EBPI) rather than "better seeds" (improving the EBPI to fit the context) [25]. Indeed, recent reviews of implementation measurement instruments [30] and implementation strategies [31] indicate that attention to intervention-level determinants has been sparse.

Implementation Strategy Usability

Implementation strategies can be defined as methods or techniques used to enhance the adoption, implementation, and sustainment of a clinical program or practice [23]. Most implementation strategies are complex psychosocial interventions that share many of the same usability pitfalls as EBPIs [23]. The development of numerous multicomponent implementation strategies has the potential to further decrease their usability in real-world contexts, inadvertently contributing to the emerging gap between implementation research and implementation practice [32]. A critical step in improving EBPI implementation is to redesign both EBPIs and their implementation supports to improve usability as well as implementation and service outcomes while retaining the effective components of each.

Human-Centered Design

Human-centered design (HCD, also known as user-centered design) has the potential to improve EBPI and implementation strategy usability. HCD is a field of science that has produced methods to develop compelling, intuitive, and easily adopted products and tools [22,33]. HCD and implementation science share the common goal of improving the use of innovative and effective practices in real-world contexts. Although implementation focuses on individuals and systems to effect change, HCD focuses on developing more usable innovations by systematically collecting stakeholder input and improving innovation-stakeholder and innovation-context fit. Although HCD is traditionally discussed in the context of digital technologies [33], HCD approaches are not restricted to technology-based solutions. Recent work has applied HCD to

EBPIs to enhance usability, decrease burden, and increase contextual appropriateness [22,34,35]. Furthermore, HCD approaches may be applied to the evaluation and redesign of implementation strategies [36,37], where the pool of potential users may also be expanded to individuals functioning in intermediary, purveyor, or other facilitative roles [38]. Overall, HCD serves as a design framework to guide the development of solutions to community-identified problems.

Study Purpose

Center Aims and Structure

The mission of the University of Washington's ALACRITY (Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness) Center (UWAC) is to study the utility of HCD as a methodological approach to improve the implementation of EBPIs in highly accessible service settings (eg, rural, urban, low-income, nonspecialty mental health). The research team reflects a diverse set of research and practice experts in mental health services, implementation science, and user-centered design. To support this mission, we created the *Discover, Design and Build, and Test* (DDBT) framework, a multiphase process that draws from established HCD frameworks [39] and applies HCD methods to modify EBPIs and implementation strategies (described below). The UWAC Methods Core will oversee, collect, and integrate data collected using the DDBT framework across all projects funded by the center. These include three primary research projects (described below), each of which will focus on the redesign of an EBPI and implementation strategy, or both. Twelve pilot projects to be funded by the UWAC via a competitive process will also employ the DDBT framework, but because these projects are not yet funded, their specifics are not discussed here. Through data collection and integration, we will address the following Method Core aims.

Identification of Evidence-Based Psychosocial Interventions and Implementation Strategy Modification Targets to Improve Learnability, Usability, and Sustained Quality of Care

During the early phases of each study, stakeholders will provide information concerning the main challenges in the use of EBPI or implementation strategy components. Components may include content elements [40] (ie, discrete tasks used to bring about intended outcomes during an intervention or implementation process) and structures [41] (ie, dynamic processes that guide the selection, organization, and delivery of content elements) that need modification as well as multilevel barriers and facilitators of EBPI implementation. Identified issues may be those that affect learnability (ie, the extent to which users can rapidly build understanding in or facilitate the use of an innovation), usability (defined previously), and quality of care (ie, delivery with fidelity and impact on target outcomes). To accomplish this aim, the UWAC Methods Core will build on the established methods of evaluating the usability of complex psychosocial interventions [34].

Developing Design Solutions to Address Modification Targets

This aim will aggregate a typology of design solutions to improve mutable EBPI and implementation strategy modification targets based on the research projects. Early work has already begun on the identification of EBPI modification types [42], and the UWAC Methods Core will extend this work to implementation strategies to create a matrix of design solutions mapped to specific modification targets.

Effect of Design Solutions on Learnability, Usability, and Sustained Quality of Care Through Changes in Modification Targets

As per the Institute of Medicine report on psychosocial interventions, the three pilot projects we specified in the center protocol will focus on developing support tools for the efficient training of frontline clinicians in EBPI elements (learnability), modifying and combining EBPI elements so that frontline clinicians serving rural and minority patients can use them effectively and with ease (usability), and developing decision support tools to assist frontline clinicians in the faithful delivery of EBPI elements without the need of expert intervention or supervision (sustained quality). A key goal of our proposed work is to determine the effects of design solutions on implementation outcomes [43] such as time to skill acquisition, sustained adherence to treatment protocol, and clinician/patient adoption of EBPI strategies. We hypothesize that core elements of the EBPI or implementation strategy can be maintained while streamlining these innovations to improve implementation and enhancing real-world effectiveness. Testing this hypothesis during the funded research projects will be the center's major contribution to the field of implementation science.

Methods

Overview

The UWAC Methods Core will achieve its aims by integrating data collected across a series of center-supported research studies. These include three studies articulated at the time of the grant submission (Table 1) as well as 12 pilot studies that will be competitively awarded over the course of the award. Table 2 shows the timeline of study activities and Center products. Multimedia Appendix 1 presents example Consolidated Standards of Reporting Trials (CONSORT) diagrams for practitioner and patient participants. The University of Washington's Institutional Review Board has approved and regulates the ethical execution of this research. Approval for the three separate studies was given on March 12, 2018 (trial number NCT03514394); March 21, 2018 (trial number NCT03515226); and March 23, 2018 (trial number NCT03516513). All participants will provide informed consent. The consent form will describe the University of Washington's policy to preserve, protect, and share research data in accordance with academic, scientific, and legal norms.

Table 1. Center project objectives and outcomes.

Project	Redesign objective	Outcomes
Project 1: Clinician Training in Rural Primary Care Medicine	Learnability	• Identification of targets for improving EBPI[a] training • Best educational strategies to address training targets • Identification of cross-cutting clinical competencies that support high-quality delivery of care versus fidelity • Measure of the impact of training modifications on clinical competency
Project 2: Usability of EBPI for Depression in Rural, Native American Communities	Intervention usability	• Uncovering usability problems clinicians experience when implementing EBPIs • Modification of EBPIs based on use challenges • Identification of usable and unusable therapeutic elements • Measure of the impact of modifications on clinical utility
Project 3: Quality/Decision Support for EBPIs in Primary Care Settings	Quality of care	• Challenges faced by clinicians when implementing EBPIs with complex cases • Novel decision support tools • Common decisional dilemmas • Accompanying expert advice

[a]EBPI: evidence-based psychosocial interventions.

Table 2. Center timeline.

Milestones	Year 1 - 2018-2019				Year 2 - 2019-2020				Year 3 - 2020-2021				Year 4 - 2021-2022			
	Q[a] 01	Q 02	Q 03	Q 04	Q 01	Q 02	Q 03	Q 04	Q 01	Q 02	Q 03	Q 04	Q 01	Q 02	Q 03	Q 04
Study #1: Learnability	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Discover	✓	✓														
Design/Build			✓	✓	✓											
Test						✓	✓	✓	✓	✓	✓	✓				
Study #2: Usability						✓	✓	✓	✓	✓	✓	✓	✓			
Discover						✓										
Design/Build							✓	✓								
Test									✓	✓	✓	✓	✓			
Study #3: Quality of Care								✓	✓	✓	✓	✓	✓	✓	✓	
Discover								✓	✓							
Design/Build										✓	✓					
Test												✓	✓	✓	✓	
Center Products											✓	✓	✓	✓	✓	✓
Typology of EBPI[b] targets											✓	✓	✓	✓	✓	✓
Matrix of targeted modifications											✓	✓	✓	✓	✓	✓

[a]Q: quarter.

[b]EBPI: evidence-based psychosocial interventions.

Project Descriptions of the University of Washington's Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults With Mental Illness Center Research

Each of the projects will focus on a different aspect of EBPI implementation and include the redesign of a patient-facing intervention, an implementation strategy, or both. In addition to their project-specific data needs, all projects will collect a common core set of data that will be integrated by the Methods Core for collective analyses. Study 1 focuses on improving learnability by implementing a novel EBPI training program to support the delivery of a manualized telephone-based cognitive behavioral therapy (tCBT) [44] by bachelor degree–level social work students who manage health care for migrant farm workers in central Washington State. Study 2 focuses on the usability of problem-solving therapy (PST) [45] and cognitive processing therapy (CPT) [46] interventions for the management of

depression and anxiety by master's degree–level social workers from seven federally qualified health centers serving Native American and frontier communities in Eastern Montana. Study 3 will address the quality of care and shared decision making by master's degree–level care managers to treat depression in urban primary care clinics in the Seattle, Washington metro area. All three studies will employ the DDBT framework. Across projects, selected EBPIs were chosen based on input from community partners and because they address aspects of common problems seen in low-income communities (especially depression and trauma).

University of Washington's Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults With Mental Illness Center Procedures: Discover, Design, Build, and Test Framework

The three-phase DDBT framework (Figure 1) is intended to gather the requisite information to drive iterative redesign of existing EBPIs or implementation strategies to improve usability and implementation outcomes (eg, contextual appropriateness, and adoption) while retaining an intervention's core components. As indicated above, DDBT is rooted in traditional HCD frameworks [39], but applies them in novel ways to EBPIs and implementation strategies. Target stakeholders (eg, clinicians, patients, and trainers) are engaged in each phase to ensure that the implementation solution meets needs of its stakeholders (ie, it is useful) and is easy to use and understand (ie, it is usable). Table 3 displays the planned data collection approaches across projects and DDBT phases. Additional human subjects and data protection details can be found in Multimedia Appendix 2.

Discover Phase

Overview

The first step of our framework leverages important aspects of HCD [39,47,48], including identification of current and potential stakeholders, their needs, influential aspects of the target setting(s), and understanding what facilitates and inhibits the usability of current tools and workflows. A design that is usable in one context, for one person, may not be usable for another person or in a different context, necessitating an understanding of the use setting in redesign efforts [49-52]. Thus, projects must use the *Discover* phase to gather information about two sets of information: the context of deployment (eg, individuals, their needs, and work settings) and information about the innovation itself (eg, usability issues), both of which are discussed below. Even if investigators enter into the *Discover* phase with a particular solution in mind (eg, expecting that a digital tool will be a useful approach to improve implementation), the appropriateness of those solutions must be continually reassessed with user input. Methodological procedures used across projects in this phase are below.

Figure 1. Discover, design/build, and test (DDBT) framework. EBPI: evidence-based psychosocial interventions.

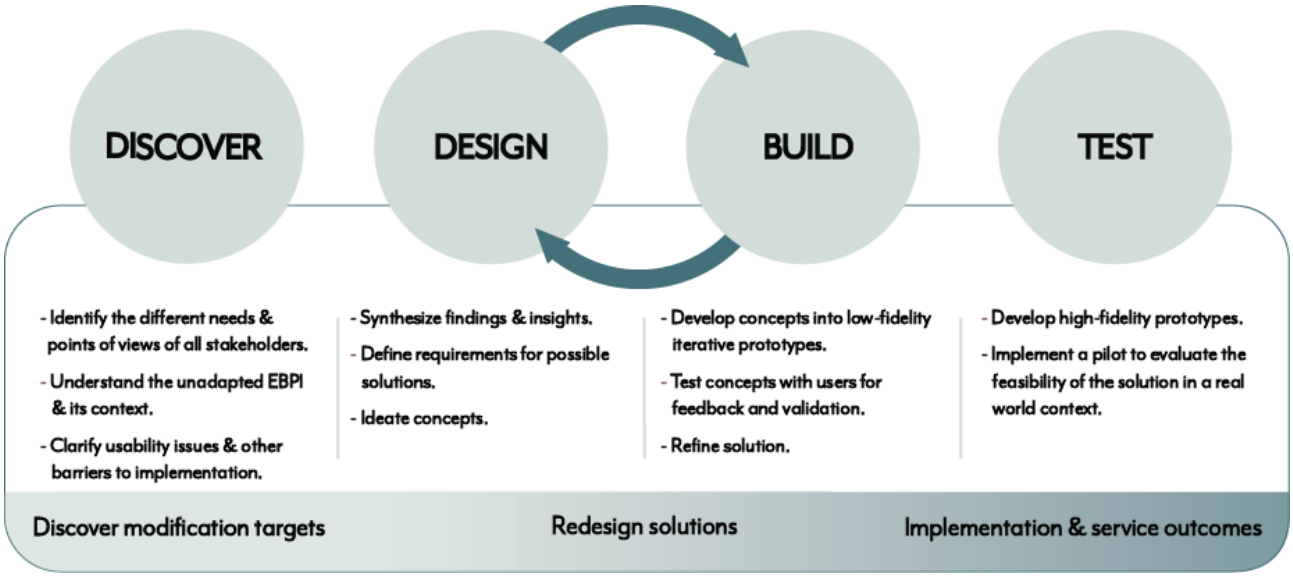

Table 3. Planned data collection across projects and DDBT (Discover, Design/Build, and Test) phases.

Projects and phases	Think aloud	Semistructured interviews	Remote survey	Contextual observation	Iterative design	As-is analysis	Cognitive walk-through	Quantitative instruments
Project 1 (Learnability)								
Discover		✓	✓			✓		✓
Design/Build	✓		✓		✓		✓	✓
Test	✓			✓				✓
Project 2 (Usability)								
Discover	✓	✓				✓		✓
Design/Build					✓		✓	✓
Test								✓
Project 3 (Quality of Care)								
Discover		✓				✓		✓
Design/Build	✓				✓			✓

Identification of Stakeholders

HCD, and hence, the DDBT framework, emphasizes explicitly identifying the range of target stakeholders to ensure new products effectively meet their needs [53,54]. Consistent with the established methods [34,55,56], each project will engage in an explicit user-identification process that includes brainstorming an overly inclusive list of potential users, articulating the subset of user characteristics that are most relevant and then describing, prioritizing, and selecting main user groups. Although we anticipate that a variety of stakeholders may be identified in each project, DDBT is most focused on gathering input from primary users [53], defined as those whose activities are most proximal to the innovation and whose needs and constraints redesign solutions must be prepared to address first. For EBPIs, primary users are most often clinicians and service recipients [22]. For implementation strategies, primary users tend to be implementation practitioners or intermediaries [57] as well as the targets of the strategy. Secondary users—who may have additional needs that can be accommodated without compromising a product's ability to meet the primary user(s) needs—may include system administrators (who often make adoption decisions) and families/caregivers among others [58]. Although primary users will be prioritized, some projects will also collect information from a subset of secondary users. Across projects, characteristics of stakeholders that might influence their experiences with EBPIs or implementation strategies (eg, previous training or treatment experiences) will be tracked to identify possible confounds.

In the learnability study (Study 1), the pool of stakeholder participants will include 15 bachelor degree-level social work students (ie, targets of the training strategy) and educators who are in the position to train these future clinicians (ie, deliverers of the training strategy). In the intervention usability study (Study 2), users will be master's degree–level clinicians who deliver behavioral health care in clinics serving Native American and frontier community members as well as representative patients from these communities. The quality of care and decision-making study (Study 3) will target both EBPI-experienced and EBPI-naive care managers in integrated primary care settings. Across studies, recruited representative users will include both those with experience in the identified intervention or strategy as well as novices to ensure broad applicability across stakeholders.

Identification of Stakeholder Needs: Semistructured Interviews, Focus Groups, and Remote Survey

All stakeholders will be observed and interviewed to identify key challenges they face in the use of EBPIs and implementation strategies. In Study 1, we will collect information from students and educators through focus groups and individual interviews about topics such as their experiences with distance learning and computerized training (implementation strategies), how they see these technologies fitting into their daily lives, and perceived utility of this form of training in addressing key issues they have experienced as novice users of EBPIs. To achieve convergence within a mixed-methods paradigm [59], we will also conduct remote, national surveys of educators and trainees to confirm the information we obtain. In Study 2, we will conduct focus groups and interviews with clinicians about the challenges they face in implementing EBPIs in rural settings, modifications they have made to EBPIs to accommodate those challenges, and reasons for EBPI de-adoption. This includes role-play observations of their modifications and the strategies they currently feel are helpful but not present in the original EBPIs. In Study 3, we will observe and interview care managers about the challenges they see with existing quality control methods and at which points in their workflows, or with which patient types, they need the most assistance. Given the importance of value alignment as a component of contextual appropriateness [60], all interviews and focus groups will also cover what the end user values about their work as service providers or implementation practitioners and suggestions for

how it could be improved, given their service context and patient population.

Contextual Observation of Stakeholders in Their Service Settings

Although qualitative interviews that clarify perceived challenges in applying EBPIs and implementation strategies are important, they are rarely a substitute for direct observation of professional behavior. Each of the primary research projects will engage in structured observations. In Study 2, for example, watching video tapes of clinician sessions and having the clinician explain their thought processes and the challenges they faced during implementation, can offer suggestions for improvement in the design of an EBPI or implementation strategy. In Study 2, the research team will also shadow representative social workers from clinics serving indigenous peoples to capture existing workflows and identify bottlenecks for implementing EBPIs. In Study 3, the research team will observe clinicians in urban primary care clinics to identify opportunities to introduce decision-support strategies.

Usability Testing via Direct Interactions With the Original Evidence-Based Psychosocial Interventions or Implementation Strategy

We will also conduct usability evaluations of each EBPI or strategy. A variety of usability testing techniques exist, which may be applied to either interventions or implementation strategies, including quantitative instruments, cognitive walkthroughs, and lab-based user testing [31,34,36,49,50]. Cognitive walkthroughs, for example, may be applied to psychosocial implementation strategies by first conducting a task analysis [61] to identify their subcomponents, prioritizing those tasks, developing scenarios to embed the tasks, walking through the tasks with users individually or in a group format, asking for ratings of the likelihood of successful completion, and soliciting "failure or success stories" that describe the assumptions underlying the ratings [62]. Another method, the "think-aloud" protocol [63,64], is a commonly employed technique in which the stakeholders verbalize their experiences and thought processes as they use a tool to complete a task during a usability testing session. For example, in Study 3, before the intervention and implementation tools are designed, the investigators must watch how key stakeholders interact with existing decision supports, including the potential use of electronic health records. In this phase, the investigators remain open to the possibility that electronic health records are the wrong design solution to provide decision support. Depending on the project, usability testing will occur with clinicians, patients, other stakeholders, or a combination.

Design and Build Phase

Overview

Based on the information gleaned from the *Discover* phase, the *Design and Build* phase is intended to iteratively and systematically develop, evaluate, and refine prototypes of interventions and implementation strategies using the techniques below. Prototyping and rapid iteration involves a process of making new ideas sufficiently tangible to quickly test their value [65]. Consistent with the HCD literature, early prototype testing based on data from the *Discover* phase is conducted with small samples (for instance, *N*=5) to answer design questions using paper versions of redesign solutions or storyboards to represent more complex psychosocial processes (eg, exposure procedures to treat anxiety and interactions between instructors and learners during training activities) [66,67]. This reduces waste of unnecessary investment in developing "high-fidelity" prototypes until as late in the process as possible.

Usability Testing

The *Design and Build* phase employs the same usability testing techniques described above in the *Discover* phase (eg, using a think aloud protocol). However, across the iterative prototyping process, this testing is increasingly summative (versus formative in the *Discover* phase) and intended to determine whether identified usability problems and contextual constraints have been addressed [49]. Therefore, usability data resulting from the *Design and Build* phase is most informative when it is compared to similar data collected previously. If intervention or implementation strategy usability has not improved over successive iterations, then additional redesign solutions may need to be explored.

Test Phase

Overview

The *Test* phase involves small-scale testing of the intervention or strategy in a form that fully functions as it is intended, with a larger number of users, and in their actual milieu. The emphasis of this testing phase is on user experience, satisfaction with the end design, reported benefit over alternative or existing processes, and implementation outcomes [43]. This includes a structured review of how the solution would fit into existing workflows within the clinical settings in which the solution is to be deployed (ie, appropriateness). To learn where the DDBT framework is helpful—or potentially harmful (changing the EBPI or implementation strategy so much that it is no longer effective)—each study funded by the UWAC will also collect the same measures in the *Test* phase, including quantitative usability evaluation instruments [34,36]. The three preplanned projects will compare the redesigned solution to the original, often in the context of small-scale hybrid effectiveness-implementation trials [68]. Across the three projects, hybrid type 1, which emphasizes effectiveness over implementation (Study 2); type 2, which equally emphasizes the two (Study 3); and type 3, which emphasizes implementation (Study 1), are represented. All patients seen in the *Test* phase of these studies will be new to the clinicians. In Study 1 (learnability), 12 students over two successive cohorts will be randomized to tCBT training as usual (original strategy) or a redesigned tCBT training that incorporates an adaptive intelligent tutoring system [69]. The intelligent tutoring system is an adaptive learning tool that bases the presentation of material on trainees' learning needs. It reflects a standardized method that can help mitigate trainee drift. Each student will see five patients (*N*=60 patients). Patient participants in this study will receive eight weekly sessions of the tCBT intervention. In Study 2 (usability), six clinicians will be randomized to either PST (original intervention; 10 weekly sessions) or the new, redesigned solution. Each clinician will

see five patients (*N*=30). In Study 3 (quality of care), six clinicians will be randomized to the usual care delivery model (intervention and strategy) or care supported by the decision-making tool. Each clinician will be assigned five patients (*N*=30) to deliver up to 10 sessions of PST.

Test Phase Measures

Data collected during the *Test* phase of the studies will inform future hypotheses about potential targets for EBPI and strategy modification. Because the UWAC studies will be small-scale randomized trials with stakeholders who were not involved in the *Discover* and *Design and Build* phases, we will have an opportunity for unbiased comparison of the identified redesign solutions. Additionally, the studies will use a common set of outcome measures in Aim 3 analyses. Because all solutions developed in this Center are aimed at enhancing usability; promoting perceptual implementation outcomes (ie, those that tend to be measured from the perspectives of critical stakeholders rather than behaviorally) such as acceptability, feasibility, and appropriateness [25] and behavioral implementation outcomes such as integrity; and containing costs, all studies will use the same usability and implementation measures. In addition, we will collect common patient-reported outcomes (eg, depression and functioning) across studies. We will also determine the need to conduct additional qualitative interviews with patients, clinicians, and implementation practitioners for the purpose of quantitative data explanation and elaboration [59] or each project.

First, three different versions of the well-established System Usability Scale [70] will be used across studies depending on whether EBPIs, implementation strategies, or traditional digital technologies are being assessed. The System Usability Scale, a widely used brief measure of the usability of a digital product, is often considered the industry standard for measuring usability. Adaptation of the System Usability Scale that will also be used across studies include the Intervention Usability Scale [34] and the Implementation Strategy Usability Scale [36] (presented in Multimedia Appendices 3 and 4, respectively).

Second, clinician and implementation practitioner perceptual implementation outcomes (ie, acceptability, appropriateness, and feasibility) will be evaluated via three recently validated instruments [71]. These include (1) the Acceptability of Intervention Measure, (2) the Intervention Appropriateness Measure, and (3) the Feasibility of Intervention Measure. These are brief, pragmatic measures that can be tailored for application to either interventions or implementation strategies and have strong internal reliability, test-retest reliability, and sensitivity to change [71].

Third, each study will collect data on the number of training hours needed before reaching adequate integrity in the EBPI or modified solution as well as the degree of sustained integrity (or integrity drift) over time. Sustained integrity in Study 1 will be measured using Cognitive Therapy Scales [72]. The PST Therapist Adherence Scale will be used to review audio sessions for Studies 2 and 3 by raters blinded to the condition. The CPT Adherence and Competence Protocol (P Nishith et al, unpublished data, 1994) will assess CPT fidelity in Study 2. Time to reach adequate integrity and sustained integrity over time will be compared between the original EBPI or strategy and the redesigned solution and combined with the cost information (below).

Fourth, implementation costs in each study will include inputs such as the time clinicians devote to learning a new technique, time experts spend delivering training, and costs of any ongoing supervision needed to mitigate skill drift [73]. These costs are relevant to both EBPI and implementation strategy redesign, as better-designed EBPIs are expected to require fewer resources to implement and better designed implementation strategies should be able to more efficiently support the learnability of EBPIs.

Finally, a variety of patient-reported outcomes will evaluate the effectiveness of redesigned EBPIs or implementation strategies. The Sheehan Disability Scale [74,75], a brief analog scale measuring functioning in work, social, and health domains will be administered to patient participants in the *Test* phase across projects. The 9-item Patient Health Questionnaire (PHQ-9) [76] measures the presence of depression symptoms over the last 2 weeks.

University of Washington's Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults With Mental Illness Data, Analyses, and Intended Outcomes

The UWAC is designed to allow for integration of data across projects to identify common EBPI and implementation strategy modification targets, develop a matrix of redesign solutions for each target, and determine if these redesigned innovations address the goals of the UWAC.

Aim 1: Identify Evidence-Based Psychosocial Interventions and Implementation Strategy Modification Targets to Improve Learnability, Usability, and Quality of Care (Discover Phase)

Discover Phase Overview

The field lacks methods for understanding usability problems of EBPIs, strategies to support these EBPIs, and methods to intentionally link EBPI usability problems to redesign targets. Aside from a few notable examples of team-based implementation approaches [77,78], there has been little systematic work explicitly involving stakeholders in the identification of EBPI modification targets, and none that use HCD methods. Similarly, researchers increasingly acknowledge the need for deliberate selection and tailoring of multifaceted implementation strategies [79] but few methods exist. During the *Discover* phase of each UWAC project, the Methods Core will employ the techniques described above (eg, qualitative interviews, focus groups, contextual observation, and user testing methods) to identify modification targets and improve strategy usability. Exploratory qualitative analysis, informed by the Consolidated Framework for Implementation Research (CFIR) [80], will allow us to identify and categorize the most critical multilevel determinants (ie, barriers and facilitators) that emerge from interviews, focus groups, and contextual evaluations that may impact implementation. Discrete usability issues—defined as aspects of the intervention or strategy that

make it unpleasant, inefficient, onerous, or impossible for the user to achieve their goals in typical usage situations [81]—will be identified for all projects and categorized within the User Action Framework (UAF) [82,83], which details how usability problems can impact the stakeholder experience at any stage of the user interaction cycle (ie, planning, translation, action, and feedback). Although the three studies have different foci, interviews across all projects will address a core set of questions guided by the CFIR and a previous framework for reporting adaptations and modifications to evidence-based interventions (FRAME) [84] (eg, "What content elements or organizing structures of EBPIs and implementation strategies are commonly identified by clinicians as needing modification?"). In addition to reporting raw data to the UWAC Methods Core, each study will report their own analyses and synthesis of usability issues and the evidence for them.

Data Analysis

Sample sizes for Aims 1 and 2 were informed by estimates from the user-centered design literature, which recommends a sample size of 5-10 to capture critical design information [66]. There is debate in the HCD literature about the appropriate sample size for user testing and growing agreement that sample size depends on the goals of the test, the complexity of its elements, and the number of groups or strata being compared [67,85]. One objective of the UWAC is therefore to pool data across projects to provide guidance for the necessary sample sizes to reach saturation for interventions and implementation strategies. We anticipate that the 12 pilot studies to be funded will propose, and ultimately work with, different sample sizes, allowing us to evaluate what sample sizes are sufficient.

Qualitative analysis will be used to identify and categorize modification targets/usability problems. Data will be organized for coding using qualitative data analysis software. Transcripts, field notes, and notes from the think-aloud sessions will be coded by two assistants. As indicated above, the CFIR [80] will guide initial analysis of contextual evaluation data and the UAF [83] will be used to categorize identified usability problems. Projects will also employ a revised version of a previous [82] augmented UAF, which includes severity ratings. In this approach, severity ratings will be given to each identified usability problem based on likelihood of a user experiencing the problem; impact on a user, if encountered; and potential for the problem to interfere with an EBPI's or implementation strategy's impact on its target outcomes. Data will be coded using an integrated deductive and inductive approach [86]. We will use existing CFIR codes, codes identified during interview development (ie, deductive approach), and codes developed through a close reading of an initial subset of transcripts (ie, inductive approach). These codes will result in themes that will provide a way of identifying and understanding the most salient strategies, structures, barriers, and facilitators within which design solutions can be developed. After a stable set of codes and themes are developed, a consensus coding process will be used [87,88]. The analysis will also assess and explore key themes that do not follow the established frameworks (eg, UAF and CFIR), looking for other guiding literature and frameworks as appropriate.

Outcomes

Integrated data analysis across projects for this aim will result in the identification of EBPI modification targets to be used in future research. An initial version of this typology will be deployed for review and additions from the field. As we discover new targets, these will be added to the matrix and made available via an online resource.

Aim 2: Develop Design Solutions to Address Modification Targets (Design and Build Phase)

Design and Build Phase Overview

Aim 2 will build on Aim 1 and aggregate a set of design solutions the Center team identifies as effective in improving modification targets across UWAC projects. In tracking all modification approaches, we will identify both the redesign solutions that advance into the final design based on iterative prototyping as well as those that are not selected. We will also explicitly assess differences in the modification targets identified for EBPIs and implementation strategies. Through this, the UWAC will be able to rapidly identify the most successful (based on user testing) design solution types for specific targets and steadily aggregate these across projects into a database to be shared with the research and practice communities.

Data Analysis

To facilitate aggregation of redesign solutions across studies, we will use FRAME [84] as a starting point for coding interventions and implementation strategies. This coding scheme identifies both content and contextual factors modified as part of the EBPI implementation, with strong interrater agreement. Using the same qualitative coding process described in Aim 1, trained raters will code design modifications according to this protocol, which will be compiled into a continuously updated database of design solutions including information about EBPI/strategy type, setting, professional characteristics (eg, clinicians and implementation practitioners), and patient characteristics. We anticipate that the database will include discrete usability problems with corresponding indicators of problem severity; aspects of the innovations and contexts for which they were identified; redesign solutions attempted; and, when available, the outcomes from the application of those solutions.

Outcomes

Aim 2 will generate the warehouse of modification targets and redesign solutions organized by modification target type and will share information about less preferred or less usable solutions (as determined by testing with stakeholders). We will make information about these design patterns available in a way that supports both searching for solutions to specific problems and browsing for design inspiration [89].

Aim 3: Determine if Design Solutions Affect Learnability, Usability, and Sustained Quality of Care Through Changes in Modification Targets (Test Phase)

Test Phase Overview

The final overarching aim of the UWAC is to test whether EBPIs and strategies modified through the DDBT Framework result

in improved learnability for clinicians and service systems, EPBI and implementation strategy usability, and sustained quality of care to deliver EBPIs in low-resource community settings. Although the principle of adapting modifiable aspects of an intervention or strategy to the needs of a setting is a central tenet of implementation science, systematic testing of adaptation mechanisms of change is new. Very little research has examined the mediating factors that are most proximal to implementation success [18]. A key goal of our work is to determine the effects of design solutions on implementation and clinical outcomes, which is critical to understanding why these solutions work or fail in real-world settings. We hypothesize that core elements and functions of EBPIs and strategies can be maintained while streamlining those innovations to improve implementation and enhance real-world effectiveness. Testing this hypothesis during the proposed and future research studies will be the UWAC's major contribution to the field of implementation science, as it will offer such a test of adaptation to local context while providing a framework for understanding the limits of such adaptation. The *Test* phase of each study is focused on gathering information (feasibility, recruitment and retention rates, response and attrition rates, etc) for future larger-scale grant applications to test the effectiveness of the adapted solutions. Thus, sample sizes were set primarily for practical reasons and driven by estimated effect sizes rather than hypothesis testing.

Data Analysis

Primary analyses focus on comparison of the key DDBT and implementation outcomes (learnability, EBPI/strategy usability, and sustained quality of care) for the original, unadapted EBPI/strategy as compared to the modified EBPI/strategy. Each project and each outcome can be summarized as an effect size (Cohen *d*) and corresponding 95% CI. There will be no subgroup or adjusted analyses. Missing data will be reported with regard to attrition and related feasibility data. Full information maximum likelihood imputation will be used for statistical analyses to include missing data, where applicable. The UWAC Methods Core will aggregate data across projects to facilitate a series of Bayesian meta-analyses. These meta-analyses will summarize the effectiveness of using HCD approaches to improve EBPIs and strategies on each implementation outcome. The Bayesian approach will allow us to adjust our inferential probability assumptions about the effects of HCD approaches on modifications. Bayesian statistics are useful even when studies are conducted in varied settings with varied scientists using varied measures, as each subsequent study represents a form of conceptual replication. Each additional study will improve our ability to draw inference (eg, "power") from the collection of studies while simultaneously preventing false alarms in individual studies resulting from random error.

Over time, we will use meta-regressions to examine the effectiveness of adaptations for particular outcomes (eg, on average, does modifying EBPI content or modifying an implementation strategy workflow have a greater impact on clinician integrity drift?), where these meta-regressions can also control for site characteristics (eg, rural vs urban). Similarly, we may be able to examine the effectiveness of specific HCD approaches (eg, the "think aloud" approach) for impacting specific implementation outcomes. The ultimate question is one of mediation: Does a DDBT-modified EBPI or strategy lead to better implementation outcomes, which in turn lead to better (larger, more rapid, or more widespread) patient outcomes? Although the initial center studies are not likely to yield large enough sample sizes to meaningfully test such an implementation mechanism question, the UWAC Methods Core will steadily aggregate data, allowing us to eventually test a range of mediation-focused hypotheses via multivariate network meta-analyses.

Outcomes

Aim 3 is centered on clinician- and patient-reported outcomes to ascertain the difference between modified EBPIs and strategies compared to treatment as usual. These pilot randomized controlled trials will generate preliminary data on learnability, usability, and quality of care to inform subsequent tests of these adaptions on a larger scale in low-resource community settings.

Results

The UWAC received institutional review board approval for the three separate studies in March 2018 and was funded in May 2018. Approvals for the 12 pilot studies are being obtained as the studies are identified and funded. At the time of publication, data collection for Studies 1 and 2 had been initiated.

Discussion

Innovation

We acknowledge that learnability, usability, and sustained quality of care are not the only important variables in the implementation of EBPIs and that intervention characteristics feature highly in implementation frameworks. To date, little work has been done to directly address EBPI or implementation strategy complexity and even less work has actively involved end users in the actual design of modifications, from beginning to end. Moreover, while the field is aware that "there is no implementation without adaptation" [25] and that EBPI characteristics drive adoption potential, no single resource or compilation of the needed targets for modification or redesign solutions is most usable by clinicians. An explicit focus on modification targets for implementation strategies is almost fully absent. Although tailoring interventions and strategies are frequently advocated in the implementation literature, specific methods of tailoring are sorely needed [79]. Very few implementation approaches attend to mechanisms of action [18,90] and even fewer attend to usability [25]. Because all UWAC studies use the DDBT framework and collect common core outcomes, we will be able to contribute substantially to the literature by providing preliminary evidence of how robust the DDBT framework is in developing EPBI and implementation strategy modifications and solutions, creating a typology of modification targets that will be disseminated publicly to facilitate future research by uncovering cross-cutting and context-specific modification needs and creating a matrix of redesign solutions matched to modification targets that will further fuel mechanistic science in implementation research.

Conclusion and Impact

Incorporation of HCD methods into implementation science has strong potential to improve the degree to which innovations are compelling, learnable, and ultimately implementable. Both fields share the common objective of facilitating the use of innovative products [22]. An extensive implementation science literature supports the importance of organizations, individuals, and contexts to the adoption and sustainment of EBPIs [91,92]. Despite a wealth of over 60 frameworks such as the CFIR [80], implementation research often assumes a relatively static innovation or implementation strategy, the high-integrity delivery of which tends to be a cornerstone of most studies. In contrast, HCD focuses primarily on the product itself, based on the assumption that a well-designed and compelling innovation is much more likely to be adopted, well-used, and sustained. The current, integrated DDBT framework draws on the strengths of each of these traditions to develop streamlined and effective EBPIs and implementation strategies. In the pursuit of integrated methods, we anticipate that the work of the UWAC will also identify a variety of barriers to integration that can be addressed as collaborative work between HCD and implementation evolves. To this end, we will build on related ongoing work to integrate these fields, such as a concept mapping study comparing HCD and implementation strategies and identifying pathways for collaboration [93]. As the science of adaptation continues to advance [94], findings yielded from the current Methods Core aims are intended to contribute significantly to both the implementation and HCD literature.

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Authors' Contributions

All authors contributed to study concept and design. PAA is the center director, led the center and design of all studies, and obtained funding. ARL, SAM, and DCA created the protocol for the Methods Core. ARL and SAM codirect the Methods Core. DCA and MDP assisted with statistical analysis planning. SAM and EF provided essential input on the methodology. ARL developed the initial manuscript outline and ARL, BNR, and PAA drafted the manuscript with contributions from all authors. All authors are contributing to the conduct of the studies and have read and approved the final manuscript for publication.

Conflicts of Interest

DCA is a cofounder with equity stake in a technology company, Lyssn.io, focused on tools to support training, supervision, and quality assurance of psychotherapy and counseling.

Multimedia Appendix 1
Example CONSORT (Consolidated Standards of Reporting Trials) diagrams for provider and patient participants in the test phase of University of Washington's Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center studies.
[PDF File (Adobe PDF File), 85 KB - resprot_v8i10e14990_app1.pdf]

Multimedia Appendix 2
Human subjects and data protection.
[PDF File (Adobe PDF File), 58 KB - resprot_v8i10e14990_app2.pdf]

Multimedia Appendix 3
Intervention Usability Scale.
[PDF File (Adobe PDF File), 26 KB - resprot_v8i10e14990_app3.pdf]

Multimedia Appendix 4
Implementation Strategy Usability Scale.
[PDF File (Adobe PDF File), 30 KB - resprot_v8i10e14990_app4.pdf]

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Abbreviations

ALACRITY: Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness
CFIR: Consolidated Framework for Implementation Research
CPT: cognitive processing therapy
DDBT: Discover, Design and Build, and Test

EBPI: evidence-based psychosocial interventions
FRAME: Framework for Reporting Adaptations and Modifications to Evidence-based Interventions
HCD: human-centered design
PST: problem-solving therapy
SUS: System Usability Scale
tCBT: telephone-based cognitive behavioral therapy
UAF: User Action Framework
UWAC: University of Washington's Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center

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Protocol

VEROnA Protocol: A Pilot, Open-Label, Single-Arm, Phase 0, Window-of-Opportunity Study of Vandetanib-Eluting Radiopaque Embolic Beads (BTG-002814) in Patients With Resectable Liver Malignancies

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Abstract

Background: Transarterial chemoembolization (TACE) is the current standard of care for patients with intermediate-stage hepatocellular carcinoma (HCC) and is also a treatment option for patients with liver metastases from colorectal cancer. However, TACE is not a curative treatment, and tumor progression occurs in more than half of the patients treated. Despite advances and

technical refinements of TACE, including the introduction of drug-eluting beads-TACE, the clinical efficacy of TACE has not been optimized, and improved arterial therapies are required.

Objective: The primary objectives of the VEROnA study are to evaluate the safety and tolerability of vandetanib-eluting radiopaque embolic beads (BTG-002814) in patients with resectable liver malignancies and to determine concentrations of vandetanib and the N-desmethyl metabolite in plasma and resected liver following treatment with BTG-002814.

Methods: The VEROnA study is a first-in-human, open-label, single-arm, phase 0, window-of-opportunity study of BTG-002814 (containing 100 mg vandetanib) delivered transarterially, 7 to 21 days before surgery in patients with resectable liver malignancies. Eligible patients have a diagnosis of colorectal liver metastases, or HCC (Childs Pugh A), diagnosed histologically or radiologically, and are candidates for liver surgery. All patients are followed up for 28 days following surgery. Secondary objectives of this study are to evaluate the anatomical distribution of BTG-002814 on noncontrast-enhanced imaging, to evaluate histopathological features in the surgical specimen, and to assess changes in blood flow on dynamic contrast-enhanced magnetic resonance imaging following treatment with BTG-002814. Exploratory objectives of this study are to study blood biomarkers with the potential to identify patients likely to respond to treatment and to correlate the distribution of BTG-002814 on imaging with pathology by 3-dimensional modeling.

Results: Enrollment for the study was completed in February 2019. Results of a planned interim analysis were reviewed by a safety committee after the first 3 patients completed follow-up. The recommendation of the committee was to continue the study without any changes to the dose or trial design, as there were no significant unexpected toxicities related to BTG-002814.

Conclusions: The VEROnA study is studying the feasibility of administering BTG-002814 to optimize the use of this novel technology as liver-directed therapy for patients with primary and secondary liver cancer.

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KEYWORDS

hepatocellular carcinoma; metastatic colorectal cancer; liver metastases; transarterial chemoembolization vandetanib

Introduction

Background

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and the fourth most common cause of cancer-related death worldwide [1]. Curative treatment options for early-stage HCC include surgical resection, liver transplantation, and ablative therapies. However, less than 30% of HCC patients are eligible for curative-intent therapies because of large tumor burden, vascular invasion, or poor liver function because of underlying liver disease [2]. For patients with intermediate-stage HCC, the current standard treatment is transarterial chemoembolization (TACE) [3,4]. Although TACE provides a survival advantage over best supportive care, it rarely produces a complete response because of persistence of viable tumor cells and is, therefore, not considered a curative therapy [5].

Colorectal cancer (CRC) is the third most commonly occurring cancer in men and the second most commonly occurring cancer in women worldwide [1]. Approximately 25% of patients present with metastatic CRC (mCRC), and approximately 35% to 55% of CRC patients will develop liver metastases at some point during the course of their disease. Surgical resection is the treatment of choice for liver metastases, offering a potential cure if they can be fully resected [6]. However, only 15% to 20% of patients that develop liver metastases will be resectable at presentation because of presence of multifocal tumors or limited hepatic reserve [7,8]. For patients not suitable for resection, TACE has been shown to be an effective treatment option, potentially offering an improvement in quality of life and overall survival. A systemic review of 13 studies, comprising 850 patients with mCRC treated using drug-eluting beads (DEB) loaded with irinotecan, demonstrated an average response rate of 56.2% by response evaluation criteria in solid tumors (RECIST) and 51.2% by modified RECIST/European Association for the Study of the Liver response criteria. The average overall survival was 16 months [9]. The improvement in quality in life is mainly related to the reduced systemic side effects of the chemotherapy drug [10,11]. DEB-TACE is, therefore, a palliative locoregional treatment option that can be considered for mCRC patients with unresectable liver metastases [12].

Compared with conventional TACE, drug-eluting beads transarterial chemoembolization (DEB-TACE) achieves higher intratumoral concentrations and lower systemic concentrations of the cytotoxic agent, thereby reducing the chemotherapy-related toxicity of treatment [13,14]. Although TACE is usually repeated multiple times, both primary and secondary liver cancers can become resistant to treatment, resulting in local progression [15,16]. There is a need to improve clinical outcomes post TACE by improving the delivery of DEB-TACE and by exploring new targeted anticancer drugs that can be delivered directly to the tumor on preloaded beads [17]. A current limitation in improving the accuracy of embolic administration during DEB-TACE and in understanding how well the treatment reaches its target is the inability to visualize the beads on imaging following local delivery within the liver. A radiopaque (RO) bead has recently become commercially available, which can be visualized with computed tomography (CT) and fluoroscopic imaging [18]. This technology has the

advantage of providing intra- and postprocedural confirmation on x-ray or CT of bead location during and after the embolization procedure, enabling real-time adjustments to optimize patient treatment [19]. The RO bead builds on existing DC Bead technology, which utilizes polyvinyl alcohol microspheres to embolize blood vessels and deliver drugs at high concentrations to tumors. The lasting radio-opacity of RO beads means that they are visible on x-ray–based follow-up scans, allowing precise evaluation of the completeness of tumor treatment.

Vandetanib is an inhibitor of the tyrosine kinase activity of vascular endothelial growth factor receptor-2 (VEGFR-2), an endothelial cell receptor for vascular endothelial growth factor (VEGF). It also possesses activity against endothelial growth factor receptor (EGFR) and REarranged during Transfection (RET) tyrosine kinases. Pathological angiogenesis is necessary for the progression of solid, malignant tumors, and inhibition of VEGF-dependent signaling has been identified as a key antiangiogenic strategy [20]. EGFR-dependent signaling is an important pathway contributing to the growth and metastasis of tumor cells, and aberrant EGFR tyrosine kinase activity has been reported in a number of human solid tumors. EGFR tyrosine kinase activity plays a key role in tumor growth and progression, including proliferation, dedifferentiation, and inhibition of apoptosis, metastasis, and angiogenesis [21].

Objectives

The VEROnA study explores the feasibility of administering a vandetanib-eluting radiopaque embolization bead (BTG-022814) [22]. It is the first time that BTG-002814 has been administered to humans. As TACE can be safely used in the preoperative setting to treat cancers before liver surgery, this study is performed in patients with resectable HCC or colorectal liver metastases before resection surgery. This provides a window of opportunity to measure levels of vandetanib in the resected liver sample as well as to assess the safety and tolerability of BTG-002814 in patients with liver cancer. As tumor recurrence rates for HCC and mCRC after resection are up to 70% [23,24], the development of a preoperative therapy, with the potential to improve long-term disease control, is an important research goal.

Methods

Inclusion and Exclusion Criteria

The VEROnA study is conducted and documented in accordance with the Declaration of Helsinki. The VEROnA study (NCT03291379) has been approved by the Health Research Authority London-Chelsea Research Ethics Service Committee (17/LO/00/11) and the Medicines and Healthcare Products Regulatory Agency (Clinical Trials Authorization number 2016-004164-19). The inclusion and exclusion criteria for the VEROnA study are summarized in Textboxes 1 and 2, respectively.

Overview of Study Design

The VEROnA study is a pilot, open-label, single-arm, phase 0, window-of-opportunity study of DEB-TACE treatment with vandetanib-eluting radiopaque beads (BTG-002814) delivered 7 to 21 days before surgery in patients with resectable liver malignancies. A target size of 6 patients with each primary diagnosis is deemed sufficient to assess safety and drug concentrations in plasma and resected specimens following treatment. As this is a single-arm study, there is no randomization. All patients are followed up for 28 to 32 days following surgery. Patients are recruited from 2 centers in the United Kingdom, and liver surgery is performed at 1 tertiary referral center. Patients are identified from regional multidisciplinary team meetings, which cover 10 referring UK centers.

Textbox 1. Inclusion criteria for the VEROnA study.

1. Male or female adults (aged ≥18 years)
2. Resectable hepatocellular carcinoma (Child Pugh A, International Normalized Ratio ≤1.5) or resectable liver metastases from colorectal cancer and a candidate for liver surgery
3. Low risk for morbidity and mortality from liver surgery
4. World Health Organization performance status 0-2
5. Adequate hematological function with hemoglobin >90 g/L, absolute neutrophil count >1.5 × 10^9/L, and platelets >75 × 10^9/L
6. Adequate liver function with serum bilirubin <1.5 × upper limits of normal (ULN), alanine aminotransferase (ALT; aspartate aminotransferase if ALT is not available) ≤5 x ULN, and alkaline phosphatase <5 × ULN
7. Adequate renal function with serum creatinine ≤1.5 x ULN and calculated creatinine clearance (*glomerular filtration rate*) ≥50 mL/min estimated using a validated creatinine clearance calculation (eg, Cockroft-Gault or Wright formula)
8. Willing to provide blood samples, and tissue samples at surgical resection, for research purposes
9. Willing and able to provide written informed consent

Textbox 2. Exclusion criteria for the VEROnA study.

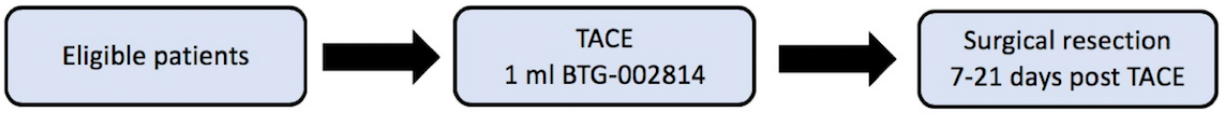
1. Any systemic chemotherapy within 3 months of the screening visit or any plan to administer systemic chemotherapy before surgery
2. Previous treatment with transarterial embolization (with or without chemotherapy) of the liver, prior radiotherapy or ablation therapy to the liver, or prior yttrium-90 microsphere therapy
3. Any contraindication to vandetanib according to its local label including:
   - Hypersensitivity to the active substance
   - Congenital long corrected QT (QTc) syndrome
   - Patients known to have a QTc interval over 480 milliseconds
   - Concomitant use of medicinal products known to also prolong the QTc interval or induce torsades de pointes
4. Any contraindication to hepatic artery catheterization or hepatic embolization procedures
5. Women of child-bearing potential not using effective contraception or women who are breast feeding
6. Confirmed allergy to iodine-based intravenous contrast media
7. Patients who cannot have computed tomography, magnetic resonance imaging (MRI), or dynamic contrast-enhanced MRI (according to site policy)
8. Active uncontrolled cardiovascular disease
9. Any comorbid disease or condition or event that, in the investigator's judgment, would place the patient at undue risk and would preclude the safe use of BTG-002814
10. Levels of potassium, calcium, magnesium, or thyroid-stimulating hormone outside the normal ranges and that in the investigator's judgment is clinically significant, or other laboratory findings that in the view of the investigator makes it undesirable for the patient to participate in the study
11. Participation in another clinical trial with an investigational product within 4 weeks before the screening visit

Protocol Treatment With BTG-002814

Following screening and written consent, all eligible patients receive 1 treatment with BTG-002814, delivered transarterially, 7 to 21 days before surgical resection of the liver (Figure 1). Moreover, 1 vial of BTG-002814, containing 100 mg vandetanib, is used for each patient. To hydrate BTG-002814, 1 mL of water for injection, followed by 9 mL of Omnipaque 350 contrast agent, is added to the vial.

Using a unilateral femoral approach, selective catheterization of the hepatic artery will be performed. Diagnostic visceral arteriography will be performed to delineate the arterial supply to the tumor to determine the presence of variant arterial anatomy and to confirm patency of the portal vein. Once the patient's arterial anatomy is understood, a catheter will be advanced into the right or left hepatic artery distal to the cystic artery (if visualized). The treatment plan will be based on the fluoroscopic appearances during arteriography. Once the catheter is in place within the artery feeding the tumor, the reconstituted BTG-002814 suspension will be slowly infused into the artery (approximately 1 mL per minute). The end point of the procedure is either full delivery of the reconstituted bead volume (ie, 1 mL vandetanib loaded beads in contrast) or near-stasis in the tumoral vessel over 6 cardiac cycles. Undelivered volume of the reconstituted embolic solution will be recorded. For HCC patients, a super selective (segmental/subsegmental) approach will be taken with the catheter placed as selectively as possible while maintaining sufficient flow to the tumor. For mCRC patients, a lobar approach will be taken.

Figure 1. Basic overview of study schema. All eligible patients are treated with 1 mL BTG-002814 (containing 100 mg of vandetanib) via drug-eluting beads-transarterial chemoembolization, 7 to 21 days before surgical resection of the liver tumor or tumors. TACE: transarterial chemoembolization.



Study Objectives

The primary aim of the VEROnA clinical study is to assess the safety and tolerability of vandetanib-eluting radiopaque embolic beads (BTG-002814).

Coprimary End Points

Coprimary end points of this study are as follows:

- Adverse events (AEs) related to treatment with BTG-002814 using the standardized grading criteria (National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 [NCI-CTCAE v4.0]).
- Concentration of vandetanib and N-desmethyl vandetanib in plasma and in resected liver tissue following treatment with BTG-002814.

Secondary End Points

Secondary end points of this study are as follows:

- Distribution of BTG-002814 on noncontrast-enhanced imaging of tumor vasculature and regions of interest using 4-dimensional (4D) CT.
- Evaluation of histopathological features in the surgical specimen (malignant and nonmalignant liver tissue): tumor necrosis, viable tumor, and vascular changes.
- Assessment of changes in blood flow on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) following treatment with BTG-002814.

Exploratory End Points

Exploratory end points of this study are as follows:

- Study blood biomarkers with the potential to identify patients likely to respond to treatment with BTG-002814
- Correlate the distribution of BTG-002814 on imaging and pathology by 3-dimensional (3D) modeling.

Study Schedule

Figure 2 shows an overview of the study schema. A baseline visit is performed up to 7 days before treatment with BTG-002814. This visit involves liver magnetic resonance imaging (MRI) scan (incorporating dynamic contrast-enhanced–MRI [DCE-MRI]) and liver CT scan (incorporating perfusion CT liver, pCT), in addition to blood samples for biomarkers. On the day of treatment with BTG-002814, pretreatment assessments include liver DCE-MRI and pCT, blood biomarker analysis, and plasma vandetanib and metabolite analysis. Following treatment, blood samples for vandetanib and metabolite analysis at 2 and 4 hours are taken. Patients are admitted overnight for observation. A noncontrast 4-dimensional CT scan is performed the following day to assess the location of beads. Blood samples are taken for biomarker and vandetanib and metabolite analysis 24 hours post treatment. Imaging with DCE-MRI and pCT is repeated on the day before surgical resection, along with blood biomarker, vandetanib, and metabolite analysis. Surgical resection of the liver tumor(s) is then conducted as part of standard clinical care. Following resection, the specimen is imaged in a micro-CT scanner before sampling for tissue vandetanib levels. Histopathological analysis is then performed. Table 1 outlines the assessments undertaken at each study visit.

Figure 2. Study schema for the VEROnA study. CT: computed tomography; DCE-MRI: dynamic contrast-enhanced–magnetic resonance imaging; DECT: dual energy computed tomography; 3D: 3-dimensional; 4D: 4-dimensional; TACE: transarterial chemoembolization.

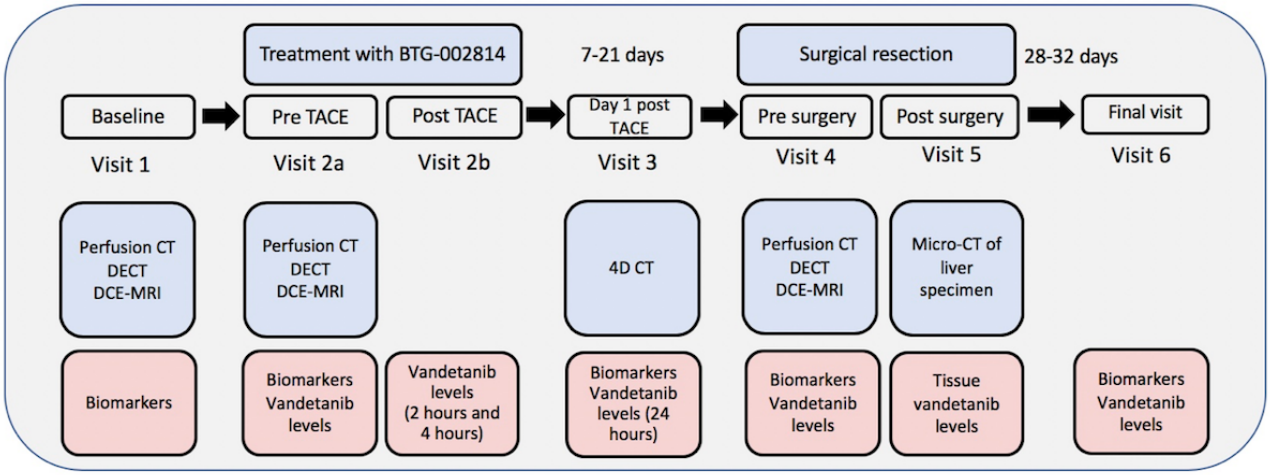


Table 1. Outline of study schedule and assessments.

Study visit and assessment	Visit 0: screening	Visit 1: baseline	Visit 2: treatment day		Visit 3: day 1 posttreatment	Visit 4: day before resection	Visit 5: surgical resection	Visit 6: end of study
			Pre	Post				
Informed consent	X[a]	—[b]	—	—	—	—	—	—
Patient demographics	X	—	—	—	—	—	—	—
Medical and prior treatment history	X	—	—	—	—	—	—	—
Eligibility assessment	X	—	—	—	—	—	—	—
Child Pugh Assessment (hepatocellular carcinoma patients only)	X	—	—	—	—	—	—	—
Physical examination	X	X	—	—	—	X	—	X
Vital signs	X	X	X	X	X	X	X	X
World Health Organization performance status	X	X	—	—	—	X	—	X
Concomitant medications	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X
Biochemistry	X	X	—	—	X	X	—	X
Hematology	X	X	—	—	X	X	—	X
Coagulation tests	X	X	—	—	—	X	—	X
12-lead electrocardiogram	X	X	X	X	—	X	—	X
Serum pregnancy test[c]	X	X	—	—	—	—	—	—
Liver MRI[d] (incorporating dynamic contrast-enhanced–MRI)	—	X	X	—	—	X	—	—
CT[e] scan liver (incorporating perfusion sequence)	—	X	X	—	—	X	—	—
4-dimensional CT scan liver	—	—	—	—	X	—	—	—
Blood biomarker analysis	—	X	X	—	X	X	—	X
Serum tumor markers	—	X	X	—	—	X	—	—
Vandetanib and N-desmethyl metabolite plasma sampling	—	—	X	X	X	X	—	X
Vandetanib and N-desmethyl metabolite tissue sampling and histopathological diagnosis	—	—	—	—	—	—	X	—

[a]Assessment performed at visit.

[b]Assessment not performed at visit.

[c]For women of child-bearing potential, a negative pregnancy test must be obtained before treatment.

[d]MRI: magnetic resonance imaging.

[e]CT: computed tomography.

Safety and Tolerability of BTG-002814

AEs and serious AEs are collected and classified according to standardized grading criteria (NCI-CTCAE v4.0) and the relationship to the study treatment recorded.

Plasma and Tissue Levels of Vandetanib and N-Desmethyl Metabolite

Vandetanib is metabolized to its major metabolite, N-desmethyl vandetanib, by cytochrome P450 3A4 (CYP3A4). Concentrations of vandetanib and N-desmethyl vandetanib in plasma and in resected liver tissue following treatment with BTG-002814 are measured and concentration profiles over time are reported.

Following surgical resection, the liver specimen is immediately secured within a plastic bag and stored on ice in an insulated container before transfer for sampling. Tissue samples are collected from the resected liver tissue to measure concentrations of vandetanib and N-desmethyl vandetanib. Samples are immediately wrapped in foil, snap frozen into liquid nitrogen, and stored at −80°C until shipped on dry ice to York Bioanalytical Solutions Ltd, York, United Kingdom, for analysis.

Blood samples for vandetanib concentrations are taken before treatment with BTG-002814 (0 min) and at 2 hours, 4 hours, and 24 hours following initial administration. If patients require a longer hospital stay, an optional additional sample is taken after 36 hours and up to the time of hospital discharge. Samples are then taken 24 hours before surgery (visit 4) and at the end of study visit (visit 6; Figure 2). At each time point for analyses, whole blood is collected into a lithium heparin tube and centrifuged. Plasma is pipetted into cryovials, which are stored at −70°C (or below) until analysis (York Bioanalytical Solutions Ltd, United Kingdom). Vandetanib and N-desmethyl vandetanib metabolite concentrations in plasma and tissue samples are determined using solid phase extraction, followed by liquid chromatography coupled to mass spectrometry (York Bioanalytical Solutions Ltd, York, United Kingdom).

Distribution of BTG-002814

Following treatment with BTG-002814, a 4D-CT scan is performed to assess the positioning of the beads. This scan is performed without contrast and is used to describe the anatomical distribution of the RO beads.

Histopathology of Resected Liver

Following liver resection, an evaluation of histopathological features in both malignant and nonmalignant liver tissue from the surgical specimen is performed. The extent of tumor necrosis, viable tumor, and any vascular changes observed are described. Conventional techniques will be used to further investigate the tumor environment, such as extent of necrosis and neoangiogenesis.

Dynamic Contrast-Enhanced–Magnetic Resonance Imaging and Perfusion Computed Tomography Imaging

As measurement of perfusion characteristics may improve understanding of liver tumor biology and behavior, patients in this study undergo DCE-MRI and perfusion CT (pCT) at time points shown in Figure 2.

Dynamic Contrast-Enhanced–Magnetic Resonance Imaging

After acquisition of standard clinical MRI liver sequences, T1 mapping is performed using 3D volumetric gradient echo imaging with varying flip angles. A series of T1-weighted 3D volumetric images are acquired at baseline and at short intervals during administration of a bolus of intravenous paramagnetic MR contrast agent. Liver parenchyma and tumor signal intensity curves are used to calculate tissue parameters describing tumor perfusion, blood flow, and vascularity using a compartment model with an arterial and portal venous input function [25].

Dual Energy and Perfusion Computed Tomography

Dual energy CT (DECT) imaging and perfusion imaging (pCT) of the liver are performed. A DECT (80 and 135 kV) and helical CT (120 kV) is acquired before contrast delivery. Following injection of iodinated contrast, volume perfusion scans are acquired. Dual energy and helical CT scans are then repeated following contrast washout. CT perfusion maps are created and used to calculate tissue parameters describing tumor perfusion, blood flow, and vascularity. Arterial blood flow, portal venous blood flow, and perfusion index will be derived using a dual input maximum slope method; blood volume and flow extraction product will be derived using Patlak analysis [26].

Blood Biomarkers

Blood biomarkers are measured to indicate potential activity of the BTG-002814. Specifically, proangiogenic factors, antiangiogenic factors, hypoxia markers, hemopoetic growth factors, inflammatory factors, and markers of endothelial function are measured at set time points during the study (Figure 2). At each study time point, blood is collected into an EDTA tube and centrifuged. Plasma is pipetted as aliquots into 6 to 8 cryovials, which are stored at −70°C (or below). Measurements of each cytokine is then performed using the Merck Milliplex kits for the Luminex 200 machine. Blood samples are also taken for the measurement of serum alpha-fetoprotein in patients with HCC, or serum CEA, CA19-9, and CA125 in patients with mCRC.

Three-Dimensional Modeling

The correlation between the distribution of BTG-002814 on imaging and within the pathological specimen will be explored using 3D modeling. Following resection of the tumor, micro-CT imaging is performed on a Mediso nanoScan Positron Emission Tomography/CT. After micro-CT, standard hematoxylin and eosin stain sections are cut from every block onto large microscopy slides. All slides are scanned and image sets are uploaded and registered using a sequential slice-to-slice image-based registration approach.

Statistical Considerations

The statistical analysis in this study is primarily descriptive, to assess the safety and tolerability of the study treatment as well as the distribution of the product following delivery. As such, the study is not powered for any statistical hypotheses. On the basis of preclinical trials, a target size of 6 patients with each primary diagnosis is deemed sufficient to assess safety and drug concentrations in plasma and resected specimens following treatment [27]. All patients who receive treatment with BTG-002814 in the study will be included in the analysis population.

Results

Enrollment for the study will be completed in February 2019. Results of a planned interim analysis were reviewed by a safety committee after the first 3 patients completed follow-up. The recommendation of the committee was to continue the study without any changes to the dose or trial design, as there were no significant unexpected toxicities related to BTG-002814.

Discussion

Overview

Although surgical treatment is the treatment of choice for HCC and CRC liver metastases, only a proportion of patients are suitable for surgery because of the presence of multifocal tumors or limited hepatic reserve [6]. TACE is the standard treatment

option for intermediate-stage HCC and is now considered a local therapy option for some patients with liver-limited mCRC. Despite recent advances in TACE delivery, including the development of DEB-TACE, tumor progression occurs in the majority of patients [15,16]. Improving administration techniques and investigating the local delivery of new anticancer drugs via TACE are important research approaches to potentially improving clinical outcomes for patients with primary and secondary liver cancer.

The ability to deliver vandetanib locally to liver tumors via TACE is a novel approach to be reported in this first-in-human clinical trial. To assess targeting of angiogenesis (via VEGF) and EGFR- and RET-dependent tumor cell growth, anticancer efficacy will be assessed in this clinical trial primarily by the extent of tumor necrosis and percentage of viable tumor in the resected liver tissue, in addition to the measurement of relevant blood biomarkers.

To date, there has been only 1 trial that has assessed the efficacy of vandetanib in HCC patients. That study, by Hsu et al, involved oral systemic administration rather than transarterial targeted therapy. A total of 67 HCC patients were randomized to oral vandetanib 300 mg (n=19), oral vandetanib 100 mg (n=25), or placebo (n=23). A total of 29 patients subsequently entered open-label treatment. Vandetanib induced a significant increase in circulating VEGF and a decrease in circulating VEGFR levels. In both vandetanib treatment arms, tumor stabilization rate was not significantly different from placebo. Although trends toward improved progression-free survival and overall survival after vandetanib treatment were found, they were not statistically significant. The most common AEs were diarrhea and rash in both treatment groups [28].

In patients with mCRC, several phase I dose escalation studies have been conducted to determine the maximum tolerated dose of oral vandetanib in combination with different therapeutic agents and regimens. These studies have reported expected and manageable toxicity profiles, but the observed efficacies have raised concern for moving forward with these combinations [29-33].

It is anticipated that the tissue concentrations of vandetanib and its major metabolite will be significantly higher in liver tumors following administration of TACE beads than following oral administration. One would speculate that the systemic concentrations of the drug should be lower following local delivery to the liver compared with oral administration, resulting in a more tolerable side effect profile, as observed in a pharmacokinetic study of BTG-002814 in a porcine model of hepatic artery embolization [27]. In this preclinical study, healthy swine were treated with intra-arterial vandetanib-eluting radiopaque beads, and tissue samples were taken from both embolized and nonembolized liver sections for determination of vandetanib and metabolite levels at necropsy (30 and 90 days). Vandetanib and N-desmethyl vandetanib were present in treated sections 30 days after administration, at levels above the in vitro IC_{50} for biological effectiveness. At 90 days, both analytes were still present in the treated liver sections but were near or below the limit of quantification in untreated liver sections, demonstrating sustained release from the loaded beads. Furthermore, intra-arterial delivery resulted in low systemic exposure, with no obvious systemic toxicity. On the basis of these data, it is postulated that, in this first-in-human study, BTG-002814 will be safe to deliver, provide sustained release of vandetanib, and have minimal toxicity from systemic exposure to drug.

Conclusions

The VEROnA study is a first-in-human, window-of-opportunity study of the safety and tolerability of BTG-002814 in patients with resectable HCC or mCRC. The study design allows translational end points to be evaluated in detail, including blood biomarkers, perfusion imaging studies, and 3D histopathological modeling.

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Authors' Contributions

RAS, SB, MC, DS, BRD, JH, ZAB, PEW, PC, MJ, and TM contributed to the study concept. All authors were responsible for writing the study protocol and standard operating procedures. LB, SF, SB, MC, JH, BRD, SR, TM, and RAS were responsible

for writing this protocol paper. SR was responsible for the statistical plan. All authors checked and approved the final version of this study.

Conflicts of Interest

RAS declares consultancy with Affidea, Astra Zeneca, Boston Scientific, BTG plc, Cancer Research Technology, DeepMind, Eisai, Sirtex, Terumo, and Varian. TM declares consultancy with BTG plc. BRD declares advisor role to Sirtex. SB declares consultancy for Angiodynamics. ZAB, PEW, SC, SR, ALL, PC, and EB are employed with BTG plc.

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Abbreviations

3D: 3-dimensional
4D: 4-dimensional
AE: adverse event
CRC: colorectal cancer
CT: computed tomography
DEB: drug-eluting beads
DECT: dual energy computed tomography
EGFR: endothelial growth factor receptor
HCC: hepatocellular carcinoma
mCRC: metastatic colorectal cancer
NCI-CTCAE v4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

pCT: perfusion computed tomography
RECIST: response evaluation criteria in solid tumors
RET: REarranged during Transfection
RO: radiopaque
TACE: transarterial chemoembolization
VEGF: vascular endothelial growth factor
VEGFR: vascular endothelial growth factor receptor

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Original Paper

Social Support and Common Dyadic Coping in Couples' Dyadic Management of Type II Diabetes: Protocol for an Ambulatory Assessment Application

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Abstract

Background: Type II diabetes mellitus (T2DM) is a common chronic disease. To manage blood glucose levels, patients need to follow medical recommendations for healthy eating, physical activity, and medication adherence in their everyday life. Illness management is mainly shared with partners and involves social support and common dyadic coping (CDC). Social support and CDC have been identified as having implications for people’s health behavior and well-being. Visible support, however, may also be negatively related to people’s well-being. Thus, the concept of invisible support was introduced. It is unknown which of these concepts (ie, visible support, invisible support, and CDC) displays the most beneficial associations with health behavior and well-being when considered together in the context of illness management in couple’s everyday life. Therefore, a novel ambulatory assessment application for the open-source behavioral intervention platform MobileCoach (AAMC) was developed. It uses objective sensor data in combination with self-reports in couple’s everyday life.

Objective: The aim of this paper is to describe the design of the Dyadic Management of Diabetes (DyMand) study, funded by the Swiss National Science Foundation (CR12I1_166348/1). The study was approved by the cantonal ethics committee of the Canton of Zurich, Switzerland (Req-2017_00430).

Methods: This study follows an intensive longitudinal design with 2 phases of data collection. The first phase is a naturalistic observation phase of couples’ conversations in combination with experience sampling in their daily lives, with plans to follow 180 T2DM patients and their partners using sensor data from smartwatches, mobile phones, and accelerometers for 7 consecutive days. The second phase is an observational study in the laboratory, where couples discuss topics related to their diabetes management. The second phase complements the first phase by focusing on the assessment of a full discussion about diabetes-related concerns. Participants are heterosexual couples with 1 partner having a diagnosis of T2DM.

Results: The AAMC was designed and built until the end of 2018 and internally tested in March 2019. In May 2019, the enrollment of the pilot phase began. The data collection of the DyMand study will begin in September 2019, and analysis and presentation of results will be available in 2021.

Conclusions: For further research and practice, it is crucial to identify the impact of social support and CDC on couples’ dyadic management of T2DM and their well-being in daily life. Using AAMC will make a key contribution with regard to objective operationalizations of visible and invisible support, CDC, physical activity, and well-being. Findings will provide a sound basis

for theory- and evidence-based development of dyadic interventions to change health behavior in the context of couple's dyadic illness management. Challenges to this multimodal sensor approach and its feasibility aspects are discussed.

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KEYWORDS

social support; common dyadic coping; type II diabetes; dyadic illness management; couples; mobile sensing; multimodal sensor data; ambulatory assessment application; MobileCoach; study protocol

Introduction

Type II diabetes mellitus (T2DM) is a common chronic disease of the endocrine system in which the pancreas no longer produces enough insulin to metabolize blood glucose or the body becomes less sensitive to insulin (ie, insulin resistance) [1]. Symptoms include numbness in the hands or feet, excessive thirst and urination, and nausea [1,2]. Worldwide, 366 million people suffer from T2DM, which corresponds to 8.3% of the world population [1]. More than 1 in 4 adults aged 65 years and older are estimated to have T2DM in the US population, resulting in 9.4% of the US population [3]. If the trend continues, 1 of 3 US citizens will have T2DM by 2050 [4]. In Switzerland, almost 500,000 people suffer from T2DM, which is approximately 4.9% of the male Swiss population and 4.2% of the female Swiss population [1,5]. The prevalence rates raise with increasing age: 15.3% of males and 11.3% of females aged older than 75 years are diagnosed with T2DM [5]. To manage blood glucose levels and reduce the risk of diabetes-related complications (eg, cardiovascular diseases, vision loss, and amputations), patients need to follow medical recommendations for healthy eating, physical activity, and medication adherence in their everyday life [3]. Most T2DM patients take oral antidiabetic drugs [6]. Diabetes management is, hence, a very complex endeavor and requires lifelong commitment and modification of one's personal lifestyle [4,7]. Evidence suggests that for married adults, illness management is mainly shared with their spouses [8,9]. Spousal involvement in patients' diabetes management may involve social support [10] and common dyadic coping (CDC) [11,12]. Until now, it is unknown which of these concepts (ie, visible support, invisible support, and CDC) displays the most beneficial effects on the diabetes management in romantic couple's everyday life when considered together. Therefore, the aim of this study is to systematically investigate the effects of social support and CDC on health behaviors involved in diabetes management (eg, physical activity, healthy diet, and medication adherence) and well-being using a novel ambulatory assessment application for smartphones for the open-source behavioral intervention platform MobileCoach (AAMC [13]) [14,15] that allows the objective evaluation of the core study constructs and outcomes in romantic couples' everyday lives.

Received Social Support, Health Behaviors, and Well-Being

Social support describes the provision of resources intended to benefit a receiver's ability to cope in times of need [16]. The most prominent functions of support are emotional (eg, comforting) or instrumental (eg, practical assistance) [17]. Recipients' reports of support received can be distinguished from providers' reports of support given [18]. The perspectives of receiver and provider do not necessarily closely correspond, even when support receipt and provision concern the same reported support from 2 different persons [19]. There is a growing body of research reporting positive associations between received support and health behaviors, such as dieting or increased physical activity in the general population (eg, studies by Scholz et al [20], Darlow and Xu [21], Courneya et al [22], and Molloy et al [23]). In the context of chronic illness, spouses or partners are mostly the main sources of support [24]. Support from spouses has been associated with positive outcomes for patients with chronic health conditions, such as healthier eating habits among diabetic patients [25], increased health behavior (eg, eating a healthy diet, engaging in physical activity, and avoiding highly stressful situations) in cardiovascular patients [26], and decreased risk behaviors in HIV patients [27]. In this research area, only few studies have examined social support and health behaviors on a day-to-day basis (for an exception, refer the studies by Khan et al [7], Iida et al [28], and Stephens et al [29]). Diabetes symptoms are very sensitive to lifestyle behaviors and fluctuate daily [30]. Therefore, T2DM offers an ideal context for investigating associations between partner involvement, well-being, and daily illness management. For example, focusing on daily processes revealed that relative to the previous day, spouses' diet-related support was associated with increases in patients' adherence to diet [29] or that daily spousal support was positively associated with patients' daily physical activity [7]. Therefore, it seems that social support provided by a partner is especially beneficial for T2DM patients' illness management.

Research on received social support and coping with stress has shown that being in a supportive relationship can buffer physical and psychological effects of illness-related stress in general [31] and regarding T2DM in particular [28]. In line with this finding, Stephens et al [29] found that spouses' diet-related support was associated with decreases in diabetes-specific distress of T2DM patients. Contrary to this result, studies on received support and indicators of well-being oftentimes result in negative associations between received support and well-being (eg, studies by Bolger et al [32], Gleason et al [33], and Seidman et al [34]). As a consequence, Bolger et al [32] introduced the dyadic concept of *invisible social support*, which is assumed to provide the benefits of support receipt without including potential costs. According to Bolger et al [32], support is invisible to recipients when the supportive acts occur outside of their awareness (ie, one partner takes care of unexpected housework without telling the other) or the recipient may be

aware of the act but may not code it as support (ie, one partner purposefully gives advice in an indirect way so as not to draw attention to the recipient's distress or his/her inability to deal with the stressful situation). To date, the few studies that have investigated invisible support in prospective diary designs (eg, studies by Bolger et al [32], Shrout et al [35], Maisel and Gable [36], and Biehle and Mickelson [37]), observational studies (eg, studies by Howland and Simpson [38] and Girmeet al [39]), and experimental designs (eg, studies by Bolger and Amarel [40] and Kirsch and Lehman [41]) have yielded support for beneficial effects on well-being and encourage further research.

The applicability of invisible support for health outcomes has been discussed (eg, studies by Kirsch and Lehman [41], Taylor et al [42], and Westmaas et al [43]). Until now, only 2 daily diary studies focused on behavioral responses to invisible support [44,45]. In single-smoker couples, higher invisible support was associated with less distress, but with more daily cigarettes smoked after a self-set quit date [44]. In dual-smoker couples only for men invisible support was associated with less distress, but not with more smoking after a joint self-set quit date [44]. Thus, based on these first 2 studies, it seems as if invisible support can also counteract the negative effects of visible support on well-being in the context of health behavior change. However, the results with the health behavior itself emphasize the need for further understanding the interplay between invisible support and health behaviors in different health contexts. Until now, no study was conducted in the context of chronic illness, and the relevance of invisible support in T2DM with regard to diabetes-related health behaviors and well-being needs yet to be demonstrated.

Most studies so far assessed invisible support by calculating a composite score from 2 self-reports (target person and partner). On the one hand, researchers assessed invisible support dichotomously (eg, studies by Bolger et al [32] and Shrout et al [35]). In this approach, invisible support was coded when the target person reported no receipt of support, but the support provider reported provision of support. On the other hand, researchers calculated continuous invisible support by subtracting received support reported by the target person from provided support reported by partners (eg, studies by Biehle and Mickelson [37] and Lüscher et al [44,45]). Instances in which the recipient reported receiving more than the provider reported giving were collapsed to zero. However, these measures are often criticized not only because invisible support is based on self-report but also because it is merely calculated and thus potentially only a hypothetical construct. Therefore, studies in which invisible support is measured directly, observed, and coded in everyday life as has already been done in the laboratory (eg, studies by Howland and Simpson [38] and Girme [39]) are strongly needed.

Common Dyadic Coping, Well-Being, and Health Behavior

The usual approach followed by social support researchers is unidirectional in that support provision of one individual (usually the healthy one), and support receipt of another individual (usually the unhealthy one) is in focus. Invisible support already introduces a dyadic conceptualization in that both perspectives of partners are usually needed for the assessment of invisible support. CDC, however, goes beyond this dyadic implementation of still individual behaviors in that CDC explicitly focuses on the joint, dyadic efforts a couple undertakes to overcome challenges and problems (eg, a study by Bodenmann [11]). There are different approaches to CDC, but all these conceptualizations share the view that CDC involves a *we* approach with regard to stress (eg, studies by Bodenmann [11], Acitelli and Badr [46], and Kayser et al [47]) and health behaviors (eg, studies by Johnson et al [48], Lewis et al [49], and Lipkus et al [50]). Thus, CDC explicitly refers to the couple's perspective and comprises joint efforts to cope with a stressor at the couple's level. In the context of diabetes management, this could mean that the couple solves all issues related to the patient's change of behavior together. Overall, research on CDC consistently results in positive associations with well-being and relationship quality (eg, studies by Bodenmann et al [51] and Traa et al [52]). Results of the association between CDC and health behavior, however, are mixed. Some studies report positive associations between CDC and health behaviors (eg, studies by Johnson et al [48] and Rohrbaugh et al [53]; for an experimental approach, refer to the study by Lipkus et al [50]). Along similar lines, within the context of T2DM, Seidel et al [9] showed that shared expectations regarding partner's diet-related involvement were positively associated with diet adherence in male patients. Benefits of a dyadic approach of patient's and partner's illness representation of T2DM were also documented by Dimitraki and Karademas [54]. Yet, another experimental study in the context of diabetes management does not support the hypothesis that CDC interventions are superior to individual interventions, albeit the dyadic group proved to be better than the control group (eg, studies by Trief [55]).

There are several ways in which CDC can be measured. The usual way of assessing CDC outside the laboratory is through self-report (eg, using the respective subscale of the Dyadic Coping Inventory) [56]. At the same time, a coding system for laboratory observations exists [56]. Another objective alternative is the assessment of we-talk by counting the use of first-person plural pronouns (eg, a study by Rohrbaugh et al [57]). Indeed, in a study by Rohrbaugh et al [57] that distinguished between we-talk and self-reported CDC, authors found that it was the objectively measured we-talk, but not the self-reported communal coping that predicted heart failure symptoms and general health. Thus, this study sets out to measure CDC with 2 assessment methods combined: self-report and we-talk on a daily basis in the context of dyadic diabetes management.

Subjective and Objective Ambulatory Assessment by Mobile Phone Apps

With regard to an in-situ assessment of the theoretical constructs of this study (ie, visible support, invisible support, and CDC), mobile phone applications are a powerful tool for several reasons [58-64]: the widespread use of smartphones and smartwatches with various sensors and touch-based graphical user interfaces makes sophisticated assessments of theoretical constructs appealing and widely applicable. Second, the combination of sensor data of smartphones and smartwatches (eg, from the global positioning system sensor or microphone) and their

proximity to their owners offers the ability to detect useful contextual information (eg, the geographic position or mood of the owner). Third, mobile phone applications are scalable, cost-effective, have low entry barriers, and are applicable to different target populations. Finally, mobile phone applications reach people in their everyday life and with an immediacy that observations using conventional research methods do not have. In recent years, researchers have increasingly begun to use smartphones and smartwatches as platforms for the assessment of health behavior. However, although there exist various mobile phone applications to monitor behaviors and outcomes related to diabetes management in general (eg, studies by Sun et al [65], Schembre et al [66], and Wang et al [67]) and individual facets of it such as physical activity (eg, studies by Joosen et al [68] and Bort-Roig et al [69]), nutrition behavior (eg, studies by Celis-Morales et al [70], Turner - McGrievy et al [71], and Hassannejad et al [72]), well-being (eg, studies by Dubad et al [73] and Servia-Rodríguez et al [74]) or conflict in couples (eg, a study by Timmons et al [75]), mobile phone applications that use objective sensor data in combination with self-reports are so far not used for the ambulatory assessment of social support and CDC.

A prominent example of a mobile phone application for the unobtrusive assessment of natural language and communication in real life is the electronically activated recorder (EAR) [76]. The EAR collects audio snippets at random times that can be coded with regard to the content of interest for the respective studies. For example, there are applications of the EAR with regard to social support provision in couples coping with breast cancer (eg, a study by Robbins et al [77]). The focus of the EAR, however, is on auditory observation only. Novel sensor–based approaches of affect recognition (eg, studies by Betella and Verschure [78], Maass et al [79], Venkatesh et al [80], van der Heijden [81], Chapaneri and Jayaswal [82], Revathy et al [83], Koolagudi and Rao [84], Heron and Smyth [85], Spanier [86], and Diener et al [87]) can be used in combination with appropriate self-report scales such as the affective slider [78] to better understand outcome parameters of well-being in the context of diabetes management.

A number of open questions remain from the current literature on visible and invisible social support, CDC, and its ambulatory assessment by mobile phone applications that will be addressed in this study. First, no study has examined the 3 concepts of visible and invisible social support and CDC in 1 study. Thus, the unique contributions of these constructs on health behaviors and well-being have not yet been examined. In particular, with regard to health behavior change, there is insufficient knowledge on the effects of invisible social support. The second open question in the current literature on invisible support and CDC concerns the assessment in everyday life. Measures of invisible support are often criticized for being not only merely based on self-report as measures of visible support but also merely calculated from independent reports of receipt and provision of support. Thus, invisible support is potentially only a hypothetical construct, and studies in which invisible support is measured directly, observed, and coded in everyday life are strongly needed. With regard to CDC, most studies so far focused on either cross-sectional associations or longer-term associations between CDC and health behavior. Associations in everyday life using an ambulatory assessment approach have been neglected so far. Given the assumed importance of invisible support and CDC for health behaviors involved in diabetes management and well-being in T2DM patients and their partners, it is of key importance to assess these constructs in a reliable and valid objective way in everyday life to further our knowledge. Third, it is still to be investigated how to design an ambulatory assessment application for the purpose of this study, which is not only accepted by study participants in their everyday situations [79-81] but also delivers high-quality data streams that are good enough or even comparable with distinct devices (eg, high-quality microphone for affect recognition from speech in the laboratory). Fourth, available speech databases and latest research on affect recognition from speech employ usually role-taking actors and thus lack natural settings and, with it, external validity (eg, studies by Chapaneri and Jayaswal [82], Revathy et al [83], and Koolagudi and Rao [84]). Finally, multimodal approaches to affect recognition are promising, but existing research is sparse, and consistent results and approaches are still to be explored [75]. This study will address all these open questions and limitations of previous research.

Aims of This Study

The aims of this study are to address the open questions outlined above. The first aim is to examine the impact of visible and invisible support and CDC on couple's dyadic management of T2DM (ie, health behaviors) and well-being. The second aim is to use an improved assessment approach of visible and invisible support and CDC in everyday life, which is based on observational and self-report data in situ instead of self-report only. The third aim is closely related to the first and second aims: that is, to develop an AAMC that allows to record both multimodal sensor data streams and self-reports related to the study's core constructs in situ to better understand visible and invisible social support and CDC and the relationship between the recorded sensor data and psychological self-reports. To better understand outcome parameters of well-being in the context of diabetes management, the fourth aim is to use a multimodal affect recognition approach (ie, speech, facial expression, and heart rate variability) in combination with self-report scales.

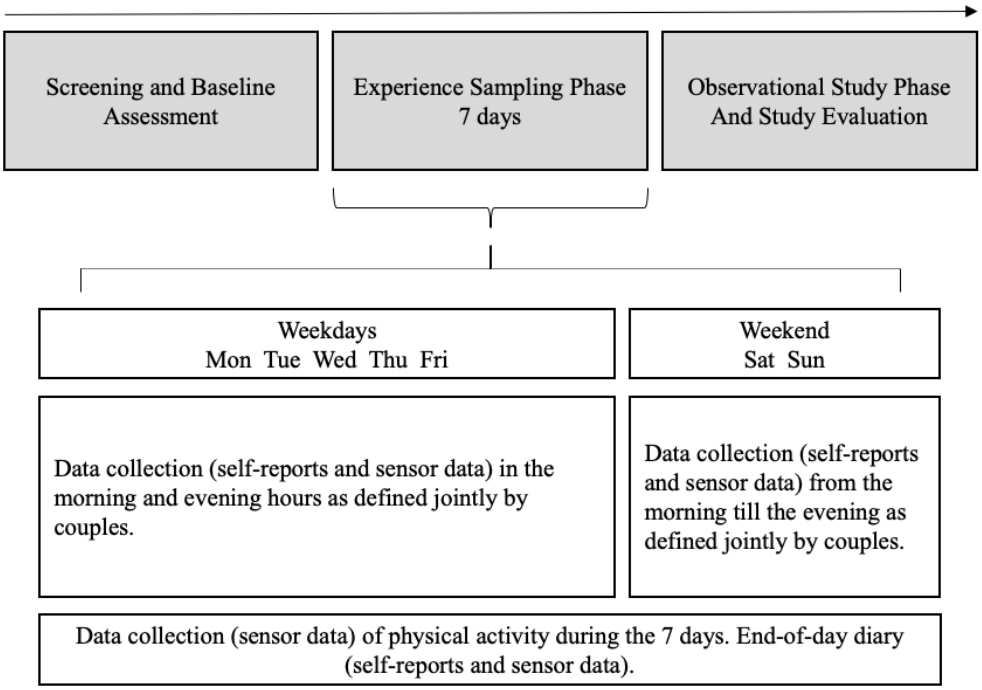
The first aim of the study will be examined in daily life as well as in an observational setting in the laboratory, whereas the second and fourth aims refer to the experience sampling phase of this study. The results of the third aim are finally used to support the first two and the fourth aims by capturing and assessing the core study constructs by self-reports and objective measures during the experience sampling phase. The following research questions result from these study objectives: (1) What are the unique contributions of visible and invisible social support and CDC for diabetes patients' health-related behaviors involved in diabetes management (physical activity, diet adherence, and medication adherence)? (2) What are the unique contributions of visible and invisible social support and CDC for indicators of well-being derived from multimodal data sources and self-reports captured by AAMC in diabetes patients and their partners?

Methods

Study Design

This study protocol describes the design of the Dyadic Management of Diabetes (DyMand) study, funded by the Swiss National Science Foundation (CR12I1_166348/1). The study was approved by the cantonal ethic committee of the Canton of Zurich, Switzerland (Req-2017_00430). To address the aims mentioned above, this study comprises an intensive longitudinal design with 2 phases of data collection. The first phase is an experience sampling phase in romantic couple's everyday life (7 days) following an ecological momentary assessment (EMA) approach [85]; the second phase is an observational study phase in the laboratory. Figure 1 shows the study design.

Figure 1. Study design.



Sample and Recruitment

The target population of this study are 180 patients with T2DM and their romantic partners. Inclusion criteria are the medical diagnosis of T2DM of the target person with prescribed oral antidiabetic drugs and having a partner of the opposite sex without diabetes or a psychological disorder who is also willing to participate in the study. The participating couples should be in a close, committed relationship for at least 1 year and living together in 1 household for at least 6 months. Exclusion criteria include T2DM treatment with insulin, inpatient treatment, shift work of one or both partners, and insufficient knowledge of the German language.

Recruitment of patients will take place in several hospitals in Switzerland. Moreover, couples will be recruited by means of flyers in medical clinics, hospitals, private practices, pharmacies, and Schweizerische Diabetes-Gesellschaft (Swiss Diabetes Society), information provided to physicians who will inform patients actively about the study, and Web-based forums for diabetes patients and diabetes-related websites. Furthermore, we plan to invite patients through radio and television formats and health magazines.

Detailed Description of the Study

Objective and self-report data from both partners are collected and assessed throughout the study to allow focusing on effects of both partners.

Screening and Baseline Assessment

Interested couples will be asked to consent to and then complete a Web-based questionnaire to screen inclusion and exclusion criteria and assess sociodemographic information. Moreover, they will receive first information about the study. Eligible couples are then invited to the laboratory of the Applied Social and Health Psychology Group at the University of Zurich for a baseline assessment. During this session, both partners will receive comprehensive information about the study, sign the informed consent form, and fill in a Web-based questionnaire capturing all constructs of interest at baseline that are not assessed on a daily basis, but will later serve as control variables. Control variables are duration of relationship, duration of living together, duration of T2DM illness, severity of illness, oral antidiabetic drugs prescribed, illness symptoms, physician's recommendations for diabetes management, and relationship quality of both partners with different dimensions such as consensus, cohesion, and satisfaction (Dyadic Adjustment Scale) [86] as well as life satisfaction of both partners (Satisfaction With Life Scale) [87], technology anxiety [88], familiarity with mobile phone text messaging applications [89], and experience

with and usage of smartphones, smartwatches, and step counting devices [80,88]. They are handed over the study smartphones (1 for each partner; Nokia 6.1, 2018, Android operating system 9.0) and the study smartwatches (1 for each partner; Polar M600, Google Wear operating system 2.3) and are instructed how to use the newly developed AAMC, which will collect the multimodal sensor data and capture self-reports of both partners of the participating couples. Moreover, during the 7-day experience sampling phase, all participants (target persons and partners) wear triaxial accelerometers at the hip (GT3X+ monitor devices; ActiGraph).

Experience Sampling Phase

The experience sampling sequence starts for all participating couples on the following Monday after baseline assessment and ends the following Sunday night to have the same sequence of days for all participants. Both partners are sent an automatically generated text message to their own mobile phones on Sunday evening and again on Monday morning reminding them to put on the study smartphones, wear the study smartwatches, and accelerometers to use AAMC directly after getting up. Participants are instructed to have all devices with them every day for the 7 days from getting up until going to bed (for a similar procedure during weekends, refer to the studies by Robbins et al [90] and Helgeson et al [91]).

The AAMC was developed as an open-source extension of the existing MobileCoach platform [13] by applying design science research. The AAMC consists of a smartphone app, a smartwatch app, and server system built on top of MobileCoach [92]. MobileCoach is a server-client system that allows both the collection of sensor and self-report data (eg, for EMA studies or for health monitoring purposes) and the delivery of health interventions [14,15]. On the server side, the data collection and intervention logic are defined (eg, when to collect which information), whereas short message service text messages and mobile phone applications for Apple's iOS and Google's Android operating systems are used to actually collect that data and deliver the interventions. MobileCoach follows the talk-and-tools paradigm [93]; that is, it provides *tools* to collect data and intervene on the one hand (eg integration of Web-based surveys or the provision of health literacy video clips) and, on the other hand, to interact with subjects through a digital coach, also known as chatbot or conversational agent [94], the *talk* component. In this study, the digital AAMC coaches PIA (interacting with the partner with diabetes) and PETE (interacting with the partner without diabetes) have been designed to talk to the subjects during the experience sampling phase with the help of a chat-based interface with predefined answer options as successfully carried out in previous work (eg, studies by Kowatsch et al [15,95]).

Design science is a methodology-guided iterative development of information systems (ISs) and rigorous evaluation of IS deployments [96,97]. During the build phases, mobile services were implemented (1) that record multimodal sensor data related to the study's core constructs through the study smartwatch, study smartphone, and a dedicated physical activity device worn on the hip and (2) that record self-report data of the study's core constructs through the smartphone.

The experience sampling is conducted as follows. A 5-min recording of audio, heart rate, gyroscope, ambient light, and accelerometer data through the study smartwatch is triggered when the partners are close to each other and when an acoustic signal of *no silence* was detected. The closeness of the partners is measured by the Bluetooth's signal strength of the 2 smartwatches. Directly after the 5-min recording, subjects are notified through an acoustic signal on the study smartphone and vibration on the study smartwatch to fill out a brief questionnaire (details are provided below) by the AAMC digital coaches PIA and PETE from within the chat-based user interface of the AAMC. If subjects do not start to fill out the brief questionnaire within 2 min, another acoustic signal and vibration are triggered. If then, within 2 min, still no response was detected, filling out the self-report is not possible anymore. During the process of filling out the questionnaire, a short 3-second video clip of the participant's facial expression is recorded with the front-facing camera of the study smartphone. The following 2 constraints were added to balance the number of sensors and self-report recordings and the burden of participants: (1) at least one recording of 5 min is conducted per hour; that is, if the recording is not triggered for 45 min as described above (ie, by the Bluetooth and acoustic signal), a backup recording is done in the last 15 min of that hour; and (2) the start of 2 recordings has to be at least 20 min apart from each other. Finally, closeness between the 2 partners is measured in a regular time interval with the help of the Bluetooth's signal strength of the 2 smartwatches during the relevant recording hours.

The relevant recording hours for this experience sampling are the hours in the morning and evening during the weekdays, that is, experience sampling days 1 to 5. These hours are defined by the couples during the onboarding process at the baseline assessment and can be set from 4 am, 5 am, 6 am, 7 am, 8 am, and 9 am to 6 am, 7 am, 8 am, 9 am, 10 am, and 11 am for the morning hours and from 4 pm, 5 pm, 6 pm, and 7 pm to 9 pm, 10 pm, and 11 pm for the evening hours. During the weekend, that is, experience sampling days 6 and 7, only the early morning hours and late evening hours are set (eg, from 6 am to 10 pm). With this procedure, privacy aspects are addressed by primarily focusing on situations, in which the couples will be spending time together and thus to reduce the number of audio recordings during the day of weekdays when chances are higher that subjects are working, moving around in public places, or visit or are visited by friends.

The brief questionnaire on the smartphone assesses patients' received and partners' provided support, CDC, and affect by valence and arousal for the past 5 min. Patients report if they received support from their partners (yes/no) and partners report if they provided support to their partners (yes/no) in the last 5 min. If the answer is yes, they are asked in what domain they received/provided support (physical activity, diet adherence, medication adherence, and other). Moreover, patients report their perception of CDC with the inclusion of other in the self-scale and the structure of interpersonal closeness [98]. Items for the partners will be directly parallel but referring to "your partner's diabetes condition." In addition, the speech recordings will be transcribed and coded or coded directly from the audio files with regard to the receipt and provision of social support

from both partners [90]. Moreover, using the system for coding dyadic coping (SEDC) [56] and the coding system of we-talk [53], the audio files will also be coded with regard to CDC. In doing so, invisible support will be identified when provided support by the partner is coded from the audio recordings, but the recipient does not report receipt of support in the subsequent questionnaire. With this method, we will be able to overcome the above-mentioned methodological problems of assessing invisible support in people's everyday life. At the same time, reports of receipt of support are the indicators of visible support. Using these different assessment methods also allows for testing the unique effects of the 3 constructs: visible support, invisible support, and CDC without running into problems of completely shared method variance.

Furthermore, the self-reported valence and arousal dimensions of affect as experienced in the last 5 min are assessed with the affective slider [78]. This affect measure is used to assess its relationship with the multimodal sensor data to derive a novel digital biomarker for affect based on voice features (eg, prosody), heart rate, ambient light, gyroscope, accelerometer data, and facial expressions [75,99]. Both self-reported affect instrument and the multimodal sensor data linked to affect will help to deepen our understanding of the outcome well-being.

On every day during the 7-day experience sampling phase, participants will also be asked by PIA and PETE from within the chat-based user interface of AAMC to complete a short end-of-day diary with more comprehensive questions on social support and CDC, healthy eating, medication adherence, and well-being of both partners to cover also the times of the day that are not captured by the random audio recordings and subsequent brief self-reports. Measures in the end-of-day diary are adapted from the studies by Bolger et al [32] received and provided *social support* is assessed by asking patients "Today, I received emotional/instrumental support from my partner" and by asking partners "Today, I provided emotional/instrumental support to my partner." Emotional and instrumental support will be briefly defined for participants. Moreover, patients will report their perception of CDC with the items (1) "When you think about problems related to your diabetes condition today, to what extent did you view those as 'our problem' (shared by you and your partner equally) or mainly your own problem?" with a bipolar response scale from 1= *today completely my own problem* to 6= *today always our problem* and (2) "When today a problem related to your diabetes condition arose, to what extent did you and your partner work together to solve it?" with a response scale from 1= *today not at all* to 6= *today very much*. Both items are adapted from Rohrbaugh et al [57] to a daily basis. Items for the partners will be directly parallel but referring to "your partner's diabetes condition." For *dietary adherence*, patients report the extent to which they had followed a recommended diet. *Medication adherence* is assessed with the Medication Adherence Rating Scale [100] adapted to a daily basis. Thereof, for dietary adherence and medication adherence, a dichotomous measure (adherence to recommendations yes-no) results. Finally, psychological *well-being* is assessed with the short form of the Positive and Negative Affect Schedule [101] and with the affective slider [78] on a daily basis of both partners. During this end-of-day diary and similar to the experience sampling procedure, a short 3-second video clip of the participant's facial expression is recorded with the front-facing camera of the study smartphone. This recording together with the additional multimodal sensor data collected over the course of the day will be used to investigate the relationship between self-reported measures of affect and well-being and the multimodal sensor data [99].

In addition to the experience sampling and the end-of-day diary, physical activity is measured continuously throughout the 7 study days with the study smartwatch and a triaxial accelerometer worn on the hip (GT3X+ monitor devices). To parallel recommendations for physical activity [102], a measure of the minutes of moderate-to-vigorous physical activity will be created by summing the minutes of moderate exercise and vigorous exercise from the accelerometer data. By doing so, a dichotomous measure (adherence to recommendations yes-no) results. Furthermore, the ActiGraph is used to validate the physical activity data of the study smartwatch with the overall objective to assess the need of a device that measures physical activity in addition to the accelerometers integrated into the smartwatches. In the best case, consistent results among the different devices would lead to a removal of the dedicated device and thus to decrease the burden of subjects in future EMA studies or health interventions.

Observational Study Phase

After the 7-day sequence, participants will return to the laboratory to hand in the study smartphones, smartwatches, and accelerometers. Moreover, couples will then participate in the second part of the study, the observational study, and complete a final questionnaire on the AAMC on their study smartphones. The observational study examines visible and invisible support and CDC by analyzing couple's videotaped discussion about diabetes-related concerns during a 10-min discussion.

Using the same procedure as was used by Dagan et al [103] and Badr et al [104], T2DM patients and their partners will be asked to list their T2DM-related and illness management–related concerns and select one that is causing them considerable distress. Next, they will be invited to discuss the issue with their partner for about 10 min in a videotaped session. The task will be guided by a psychologist who will leave the room during the discussion. The underlying idea is that the discussions will capture how couples talk about T2DM-related concerns. During the discussion, each partner will wear a smartwatch as it collects various sensor data similar to that in the ambulatory setting for the experience sampling phase. Following the discussion, both partners will report their perception of the discussion, and both partners will rate the discussion in terms of the degree to which it has been typical of their discussions at home, how helpful it was, and how it made them feel. Furthermore, both partners will complete measures on how much they felt supported and how much they were themselves providing support. This allows the assessment of invisible support by coding provision of support and self-reported receipt of support [38,39]. Also, they will each complete the Affective Slider self-report, assessing the valence and arousal dimensions of their affect over the last 10 min of the discussion. The videotaped discussions are

subsequently coded by trained observers for visible and invisible support transactions and CDC. For this, a codebook will be developed based on previously published work for visible and invisible support [38,39,104,105]. We will use the SEDC [56] for coding CDC. Moreover, 2 trained blinded coders, showing high interrater reliability (kappa) after training, will review the videotaped discussions for the support provided (observer-rated support) and dyadic coping strategies independently. This procedure will not only consider both perspectives of social support of a couple but also an observer perspective as suggested by Dunkel-Schetter et al [19].

Finally, couples will complete separately from each other a Web-based survey on technology acceptance constructs with regard to AAMC such as perceptions of enjoyment, ease of use, usefulness, and the intention to interact with the digital AAMC coaches PIA and PETE [80,94,106-109]. In addition, consistent with previous research on technology acceptance, 7-point Likert scales ranging from strongly disagree (1) to strongly agree (7) will be used. To assess the attachment bond of the participants with the digital coaches PIA and PETE and also the shared understanding between them and subjects with respect to the EMA goals and tasks, a short version of the working alliance inventory for technology is adopted from previous work [110-113]. In particular, we will use the Session Alliance Inventory by Falkenstro¨m and Hatcher [113] with 6 items because of the short duration of the EMA study with a 6-point response scale ranging from not at all (1) to completely (6). Finally, subjects are asked to indicate potential improvements related to the AAMC. All the couples will receive a compensation of CHF 100 for their time and travel expenses.

Statistical Analysis

The main research aims of this study refer to between-person associations of visible support, invisible support, CDC, patient's diabetes-related health behavior, and well-being of both partners using a dyadic approach to account for the interdependence among couple members using a 2-level statistical model for distinguishable dyads as indicated for patient-partner dyads [114]. The main analyses will be correlations and multiple regression analyses, which will be performed in SPSS and R. For the diabetes-related health behaviors, which relate to physical activity, diet, and medication adherence, we will generate a daily composite score, indicating the meeting of the recommendations for all 3 behaviors together ranging from 0 (meeting none of the recommendations) to 3 (meeting all of them). Moreover, we will also be able to analyze associations between predictors and the different behaviors assessed continuously in separate analyses. The idea of the composite score, however, takes into account that the real-life assessment method we chose to capture invisible and visible support and CDC using objective measures might result in highly ecologically valid and reliable measurements, but potentially in a rather low frequency of these predictors for the different diabetes-related health behaviors. With regard to well-being, we will consider the affective valence and arousal assessed during the experience sampling sequences or the mean scores of positive and negative affect from the end-of-day assessments. On a more exploratory level, we will also analyze day-to-day within-person and within-couple associations in further analyses using multilevel modeling. But because of the novelty of our approach and the rather short time frame of 7 days, this will not be the main focus.

To assess the relationship between the sensor data and self-reports, machine learning is applied, which is carried out in several steps. First, preprocessing of the raw sensor data involves feature extraction, feature scaling, feature selection, and dimensionality reduction. The resulting features derived from sensor data will be tested in machine learning models to predict self-reported affect and well-being. Second, the data will be split into training and test datasets to assess how derived algorithms generalize to new data [115]. The training dataset will also be split into subsets, where a k-fold cross-validation will be applied. The performance of the resulting model will then be evaluated using the test data set. This procedure will be repeated for various learning algorithms (eg, random forest, support vector machines, naive Bayes, recurrent neural networks, and feedforward neural networks). After comparing the performance across algorithms, the best overall model will be selected. We expect to produce a model that efficiently predicts affect and well-being using a multimodal compared with a unimodal approach as outlined in previous work on affective computing [99].

Power Analysis and Sample Size

The sample size was calculated based on Cohen [116] and using the G*Power program [117] to secure adequate power for the primary outcomes. There are no meta-analyses available for the associations between visible support, invisible support, and CDC with health behaviors and indicators of well-being. Moreover, studies reporting results from diary studies use unstandardized effects. Thus, we base our power calculation on data from previous studies on these associations, but we are aware that the data basis is somewhat unsatisfactory to make strong conclusions about the expected effect sizes. Previous studies reported varying effect sizes for visible received support on health behavior (eg, r=0.29-0.34) [20,23]. There are only 2 studies so far that examined the association between invisible support and health behavior (eg, smoking) [44,45]. In these 2 studies, however, no standardized effect sizes are available because of the focus of within-person effects. In the case of visible and invisible social support and their relations to well-being, we draw on the experimental evidence available [40]. In a series of 3 experiments, Bolger and Amarel [40] demonstrated that visible support compared with a no-support control group was related to increases in distress (d=0.27 and d=0.66, ranging from small to medium effect sizes). Invisible support, in contrast, leads to lower distress (d=−0.63 and d=−1.09, indicating medium to large effect sizes). The difference between the effects of invisible and visible support resulted in a large effect (d=−1.09). Thus, medium effect sizes for the associations between visible and invisible support and indicators of well-being will be expected. In the case of CDC, previous studies report effect sizes with behavior of r=0.20 with exercise adherence, r=0.20 with dietary adherence in a sample of diabetes patients [48]. Moreover, in the domain of well-being, effect sizes range from r=0.20 to r=0.33 (eg, a study by Badr et al [118]).

As we will not only address bivariate associations between our predictors and criteria but aim at comparing effects between our predictors, our calculation of the power is based on a 2 dependent Pearson r's analysis with a common index. To the best of our knowledge, no published data on the intercorrelations of visible support, invisible support, and CDC are available. Data from our own research with smoking-nonsmoking couples (excluding CDC) resulted in an association of r=−0.25 for visible and invisible support. To detect a significant association with a continuous outcome at P<.05 with a power of 1−beta=0.90, and assuming a small effect size of r=0.2, for health behavior and visible support, r=−0.2, for health behavior and invisible support and an intercorrelation of r=−0.25 between visible and invisible support, the required sample size is 164. Because effect sizes for CDC tended to be higher, the study will be powered for the smaller effect sizes of support. Previous studies applying intensive longitudinal designs resulted in very low rates of dropout even across a longer period (ie, ≤10%) [119-121]. This can be explained with a high commitment in couples willing to participate in these kinds of studies. On the basis of this experience, we will add 10% to the calculated sample size to account for potential dropout. This results in a total required number of 180 couples.

Analyses of the relationship between multimodal sensor data and self-reported data on affect and well-being are conducted with the help of machine learning. We estimate that in the best case, we will have an average of 10 completed self-reports per day for all 7 days resulting in 25,200 samples (360 individuals×10 self-reports×7 days). It is highly likely to have missing data if subjects do not complete the self-reports. Therefore, in a worst-case scenario with only 1 self-report completed per day and a corresponding 90% missing data, there will be 2520 observations left to use to train the machine learning algorithm. Owing to the fact that there exists no widely accepted sample size calculation method for machine learning approaches, the sample size of 360 individuals with up to multiple measurements on 7 consecutive days (eg, at least 2520 observations only from the end-of-day diary) lies above related work (eg, studies by Wahle et al [60] and Timmons et al [75]) and thus is assumed to be adequate for the purpose of this study.

Data

In line with the open research data initiative of the Swiss National Science Foundation, the anonymized data of the study will be made public in a noncommercial database for replication purposes of the analyses, additional data analyses by any third parties (eg, other research groups), and quality control purposes, given that there are no ethical or legal restrictions.

Results

The AAMC was designed and built until the end of 2018 and internally tested in March 2019. In May 2019, the enrollment of the pilot phase began. The data collection of the DyMand study will begin in September 2019, and analysis and presentation of results will be available in 2021.

Discussion

The impact of social support and CDC on health behavior change and well-being has attracted researchers' interests for some time. Researchers found that social support and CDC are associated with benefits for health behaviors and well-being (eg, studies by Scholz et al [20], Stephens et al [29], Johnson et al [48], Bodenmann et al [51], Rohrbaugh et al [53], and Uchino et al [122]) but often also with costs and harmful consequences (eg, studies by Bolger et al [32], Gleason et al [33], Seidman et al [34], Westmaas [43], and Trief [55]). For further research and practical reasons, it is crucial to identify which types of social support and CDC are beneficial and which are potentially harmful for health behaviors and indicators of well-being. Diabetes management is an ideal field to tackle this task. T2DM is a widespread disease and can be treated and managed by following a healthy meal plan, regular physical activity, and taking medications to lower blood glucose levels. Thus, patients' education and self-care practices are important aspects of T2DM management that help patients to stay healthy. The social environment has been found to be highly influential in the illness management process [10,11] although effects of social support and CDC on health behavior change and well-being in the context of T2DM management are not yet well understood. This study is the first to systematically investigate couples' dyadic illness management by investigating visible and invisible support and CDC in T2DM patients and their partners in daily life by applying an experience sampling approach and an observational approach on the basis of the new open-source behavioral intervention platform MobileCoach [14,15].

This combined experience sampling and observational approach is highly relevant for the following reasons: analyzing visible and invisible support and CDC in daily life has thus far not been done with a focus on a dyadic perspective by considering T2DM patients and their partners. Furthermore, so far it is unknown which of these concepts displays the most beneficial associations with well-being and health behavior when considered together. Moreover, measurement of these constructs in people's everyday life is by self-report only. Current technical developments allow using alternative, more objective operationalizations of these constructs and solve problems linked to self-report instruments. However, with the method applied in this study, we will not be able to capture all forms of invisible social support. For example, all kinds of nonverbal support behaviors, such as hugging as a form of emotional support, will not be detected. Nonetheless, we consider this assessment method innovative and advantageous to mere self-report measures of invisible support. Furthermore, this study will not only substantially advance the knowledge in the area of couple's dyadic management of T2DM but also on the important question of which supportive or coping acts are positively related to health behavior change and well-being. Therefore, this will provide a sound basis for the development of theory-based and evidence-based dyadic interventions to change health behavior.

Furthermore, the technical contribution of this project, that is, the enhancements of the MobileCoach platform with its newly developed modules (AAMC) and its capabilities to capture

subjective self-report data and objectively physical activity and affect through a multimodal sensor fusion approach, will be made open source under the research and industry-friendly Apache 2 license [123]. Thus, we expect high adoption rates and further developments of the AAMC by public institutions, business organizations, and interdisciplinary research teams in the field of ISs, computer science, health psychology, and behavioral medicine. The AAMC is generic in that it may not only be suitable for diabetes management but also for related diseases such as obesity, hypertension, or mental health disorders in which self-reports, physical activity, and affect detection take over a key role for diagnosis and health intervention designs. Moreover, given a sufficient degree of classification accuracy in using sensed and EMA data to predict affect and well-being, these models could then be used to help reach vulnerable individuals early and provide appropriate just-in-time adaptive interventions [124], respectively.

There are several issues that might raise questions on the feasibility of this study. First, speech recordings have repeatedly been questioned with regard to research ethics because it might happen that people not involved in the research study are being recorded too or that participants' privacy is endangered. With regard to protecting participants' privacy, for example, all participants have the opportunity to listen to their audio files and request their deletion without giving any reason and without anyone else listening to them as already applied by Robbins et al [77,90]. Moreover, with regard to the recording of other people than the participating couple who did not provide informed consent, the following steps will be taken: First, participants will be advised to wear a small badge signaling that audio recording might happen as applied by Robbins et al [77,90]. Second, identity of anyone else than the partner will not be possible to be detected by the study personnel. Thus, anonymity will be granted.

Every study applying intensive longitudinal data assessment in people's everyday life faces the challenge to potentially overburden participants resulting in high rates of refusal to participate or high attrition rates. There are studies using an intensive data assessment in diverse populations, demonstrating that studies similar to this one are feasible (eg, a study by Helgeson et al [91]); adolescent diabetes patients completed a 3- to 5-min questionnaire on the palm pilot every 2 hours throughout the day over a 2-day weekend, without increasing participants burden to the point of noncompliance). Another important challenge of this study regards the time-consuming and labor-intensive process involved in handling the large volumes of audio and video data. It is possible that as technology further develops, there will be the opportunity to make use of advanced speech recognition software; however, such software is not yet sophisticated enough to pick up on fineness of social interactions in romantic couple's everyday life.

Using AAMC methodology will make a key contribution with regard to the objective operationalizations of social support, CDC, and physical activity, and thus, we will be able to provide detailed characterization of romantic couple's communication about their dyadic diabetes management in daily life. To deepen the understanding of when social support and CDC are particularly effective, the data recorded with the AAMC will also be used to detect affect by a multimodal sensor fusion approach. The results of this study will provide a sound basis for the theory- and evidence-based development of dyadic interventions to change health behavior in the context of couple's dyadic illness management. Implications may include exploring opportunities for the use of the AAMC methodology and inform other areas of couple's everyday illness management of other chronic illnesses.

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Authors' Contributions

US and G Bodenmann are the principal investigators of the study. US and JL developed the study design together. The design of the EMA logic (Bluetooth and acoustic pattern triggered recordings of the multimodal data sources) and the incorporation of the multimodal approach to affect detection was designed by TK, G Boateng, and PS. JL coordinates the study. JL drafted the manuscript. US, TK, G Boateng, PS, and G Bodenmann contributed to the manuscript. All authors read and approved of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Existing peer-review reports from the Swiss National Science Foundation.
[PDF File (Adobe PDF File)481 KB - resprot_v8i8e13685_app1.pdf]

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Abbreviations

AAMC: ambulatory assessment application for the open-source behavioral intervention platform MobileCoach
CDC: common dyadic coping
EAR: electronically activated recorder
EMA: ecological momentary assessment
IS: information system
SEDC: system for coding dyadic coping
T2DM: type II diabetes mellitus

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Protocol

Effectiveness and Cost-Effectiveness of Blended Cognitive Behavioral Therapy in Clinically Depressed Adolescents: Protocol for a Pragmatic Quasi-Experimental Controlled Trial

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Abstract

Background: Cognitive behavioral therapy (CBT) is an effective intervention to treat depressive disorders in youth. However, 50% of adolescents still have depressive symptoms after treatment, and 57% drop out during treatment. Online CBT interventions have proven to be effective in reducing depressive symptoms and seem promising as a treatment for depressed adolescents. However, combining online programs with face-to-face sessions seems necessary to increase their effectiveness and monitor for suicide risk.

Objective: In this study, we examine the effectiveness and cost-effectiveness of a blended CBT treatment protocol, a mixture of online and face-to-face CBT, as a treatment for clinically depressed adolescents.

Methods: A pragmatic quasi-experimental controlled trial will be conducted to study the effectiveness of a blended CBT treatment protocol, in which blended CBT is compared with face-to-face CBT (n=44) and treatment as usual (n=44); the latter two were collected in a previous randomized controlled trial. The same inclusion and exclusion criteria will be used: adolescents aged between 12 and 21 years, with a clinical diagnosis of a depressive disorder, and referred to one of the participating mental health institutions. Assessments will be conducted at the same time points: before the start of the intervention, during the intervention (after 5 and 10 weeks), postintervention, and at 6- and 12-month follow-ups.

Results: The primary outcome is the presence of a depression diagnosis at 12-month follow-up. Several secondary outcomes will be measured, such as depressive symptoms, quality of life, and suicide risk. Costs and effects in both conditions will be compared to analyze cost-effectiveness. Further, moderating (age, gender, alcohol and drug use, parental depression, and other psychopathology) and mediating effects (negative automatic thoughts, cognitive emotion regulation, attributional style) will be analyzed. Also, treatment characteristics will be studied, such as characteristics of the therapists, treatment expectancy, and therapeutic alliance. Dropout rates and treatment characteristics will be measured to study the feasibility of blended CBT.

Conclusions: This study will examine the effectiveness and cost-effectiveness of a blended CBT program in which depressed adolescents are treated in mental health care. Results of blended CBT will be compared with face-to-face CBT and treatment as usual, and implications for implementation will be reviewed.

Trial Registration: Dutch Trial Register (NTR6759); http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6759

International Registered Report Identifier (IRRID): DERR1-10.2196/13434 RR1-10.2196/12654

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KEYWORDS

depression; major depressive disorder; cognitive behavioral therapy; blended; eHealth; online; adolescents; effectiveness; cost-effectiveness

Introduction

Depressive disorders are among the most prevalent mental health disorders in adolescents [1]. They have a substantial effect on well-being, a high burden of disease, and a high risk of recurrence and chronicity [1,2]. At the age of 18 years, more than 15% of adolescents have suffered from a major depressive disorder [3]. Depression shows high comorbidity with other mental health diagnoses and increased social problems, decreased academic performance, increased school dropouts, more substance abuse, and an increased risk of suicide attempts and suicide [1,2,4]. Therefore, it is crucial that depressive disorders are treated effectively at an early age. In this study, we will test the effectiveness and cost-effectiveness of a blended treatment protocol [5] that combines internet-based and face-to-face sessions in an integrated treatment protocol targeting depressive symptoms in clinically depressed adolescents.

Several meta-analyses have shown that cognitive behavioral therapy (CBT) is an effective intervention to treat adolescent depression [6,7]. However, the effect size of CBT was found to be moderate (Cohen's *d*=0.53) [7], and 50% of the adolescents were not free of depressive symptoms after being treated [8]. A recent Dutch randomized controlled trial (RCT) showed that the D(o)epression protocol (face-to-face individual CBT) was equally effective as treatment as usual (TAU; for example, interpersonal therapy, family therapy, medication, mindfulness training, creative therapy, and running therapy) in reducing depressive symptoms, as assessed by the Children's Depression Inventory 2, and depressive disorders, as assessed by the semistructured interview Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [9,10]. Despite this result, a significant number of adolescents were not free of depressive symptoms at posttreatment (24%), the effects were moderate, the dropout was high (57%), and it was hard to motivate patients to finish the treatment. Therefore, it is important to develop an attractive and more suitable treatment for adolescents who do not prefer to visit a mental health professional each week. Exploring possibilities to improve existing treatments in an innovative manner with recently developed technologies to reach out to patients may prove a fruitful strategy.

One way to improve the flexibility and attractiveness of treatment of depressed adolescents is to offer online CBT. Earlier research showed that online CBT and face-to-face CBT had, on average, similar effects in the treatment of depressive disorders in adults [11-14]. It is suggested that online interventions can increase treatment motivation and expectancies for some patients and might decrease resistance because they can be easily tailored to the adolescents' needs and adjusted to their daily lives [15]. Another benefit is that online interventions seem more easily accessible for adolescents. Only 25% of the adolescents who suffer from depression receive treatment, so improving access to treatment is crucial [16]. Furthermore, adolescents appear to prefer to work autonomously on their treatment, which is typical for online interventions [15]. Online interventions increase independence and self-confidence of patients because patients can choose when and how often they work on the intervention. It also strengthens their competences [17] and can enhance social support by peers through online chat [18]. For these reasons, online CBT is a promising intervention.

However, when treating depression, face-to-face contact with therapists is strongly advised because the suicide risk has to be monitored. Therefore, treatment that is only offered online, such as online CBT, might not be sufficient for depressed adolescents. There are several therapist-supported options that can be combined with online treatment. Some treatment protocols offer online CBT combined with support or guidance by a therapist through encrypted email or online chat, called guided CBT. Several systematic reviews found that therapist guidance in guided or blended CBT increases the effectiveness of online interventions and is also associated with higher completion of the treatment [11,12,19]. The so-called blended treatment protocols could even be more appropriate or adequate for depressed adolescents. In blended treatments, the online protocol and face-to-face sessions are fully integrated into one treatment protocol. These blended treatment protocols might contain the optimal combination of flexibility and attractiveness for adolescents and possibilities to monitor progression and risk for therapists during the face-to-face sessions.

Health care costs of depression treatment could potentially be reduced by offering CBT in a blended form compared with face-to-face CBT or TAU because some face-to-face sessions with a therapist are replaced by an online program. Fewer face-to-face sessions per patient are needed; therefore, therapists can treat more patients, which in turn can decrease the duration of waiting lists [17]. Both improving access and reducing waiting lists might allow more patients to benefit from treatment and, eventually, societal costs may be reduced as well [20]. In sum, blended treatment, defined as a combination of online treatment and face-to-face sessions, might be the solution to optimize the effectiveness of CBT for depressive adolescents by increasing motivation and expectancy, decreasing resistance (and dropouts), and tailoring the treatment [15,17], which will likely lead to reduced costs [20]. However, the effectiveness has never been studied before in clinically depressed adolescents who are referred for treatment [21]. The treatment protocol D(o)epression Blended was specifically developed to treat depressive disorders in clinically referred adolescents [22].

This study will examine the effectiveness and cost-effectiveness of D(o)epression Blended compared with D(o)epression face-to-face and TAU in clinically depressed adolescents. The adolescents in the latter two conditions already participated in a previous study comparing CBT with TAU using an RCT design [9,10]. Blended CBT treatment is expected to be more effective than TAU. Additionally, we expect blended CBT to be equally effective as face-to-face CBT. We also will study the intervention effect of depression severity, quality of life, suicide risk, and comorbidity. The costs of the interventions in the three conditions will be compared to analyze the cost-effectiveness. In addition to examining the effectiveness and cost-effectiveness, we will examine who the intervention is effective for by testing several moderators (age, gender, ethnicity, family income, alcohol and drug use, life events, degree of conflicts, parental depression, and other psychopathology) and how the intervention works by studying several mediators (negative automatic thoughts, cognitive emotion regulation, attributional style). Furthermore, treatment characteristics will be studied; that is, characteristics of the therapists, treatment expectancy, previous treatments, treatment satisfaction, therapeutic alliance, cooperation with treatment, and dropout rates to see whether the feasibility of D(o)epression Blended differs from face-to-face CBT and TAU, and whether these factors are related to the implementation and execution of the treatment program.

Methods

Design

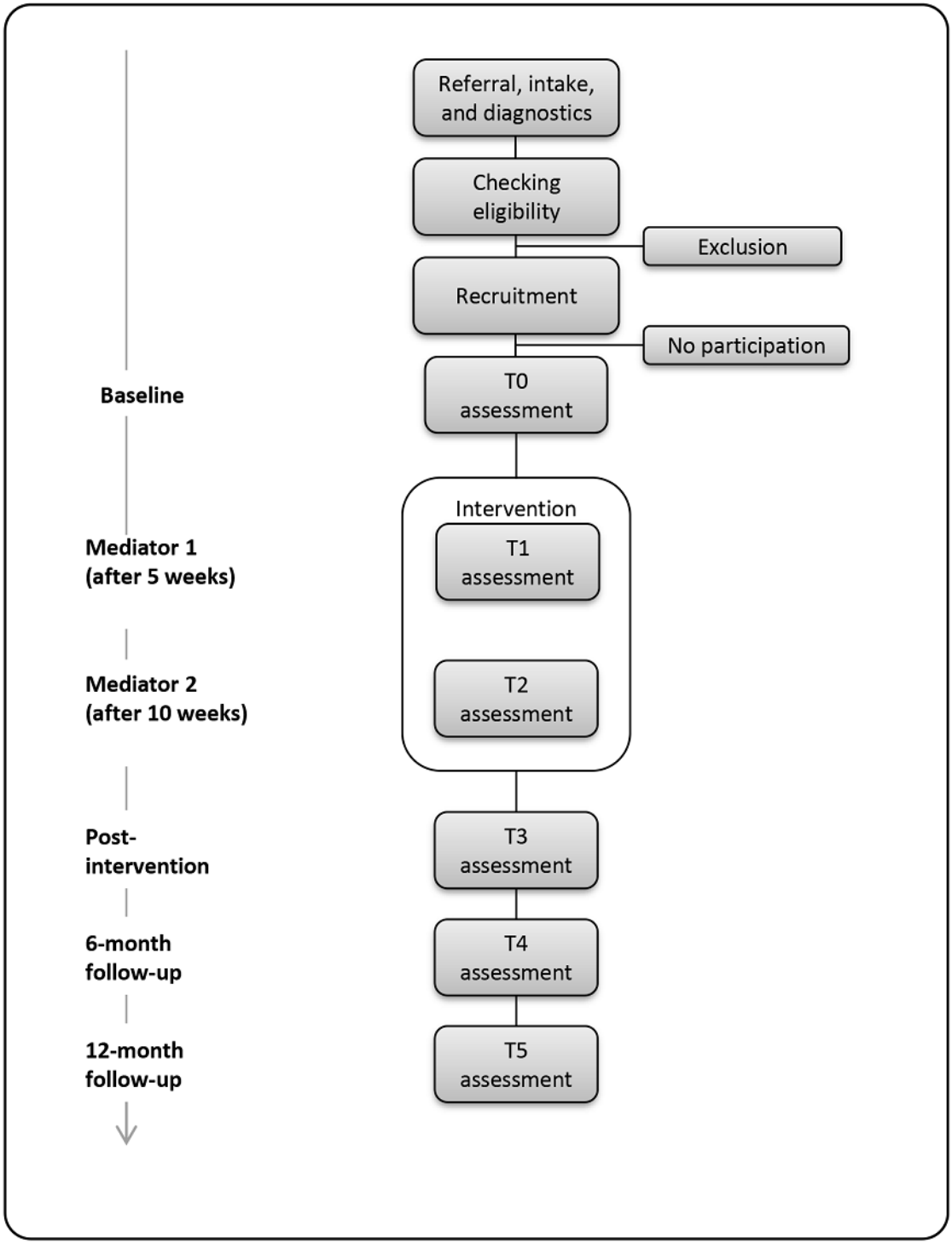
This study will use a pragmatic quasi-experimental controlled trial design with one condition to evaluate the effectiveness and cost-effectiveness of blended CBT. Data from a previously conducted RCT, in which face-to-face CBT was compared to TAU, will be used to compare the different treatments. Therefore, this can be seen as a third additional condition to the previously conducted RCT.

A new cohort will be measured and treated in this study. The assessments and instruments will be identical to the previous study comparing CBT to TAU. Assessments will be conducted at baseline (T0), during the intervention after 5 weeks (T1), during the intervention after 10 weeks (T2), at 1 to 4 weeks postintervention (T3), at 6 months follow-up (T4), and at 12 months follow-up (T5). The overall study design is shown in Figure 1.

For the adolescents, it will take an estimated 60 minutes for T0; 40 minutes for T3, T4, and T5; and 30 minutes for T1 and T2. For parents, the measurements will take an estimated 45 minutes for T0, T3, T4, and T5, and an estimated 5 minutes for T1 and T2. For the therapist, T0 will take 3 minutes, and T1, T2, and T3 will take 1 minute to complete. Time estimations are based on earlier studies [10].

The study was approved by the medical ethics committee of the University Medical Centre Utrecht in the Netherlands (NL61804.041.17). Details are described according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [23]. The study was registered prospectively in the Dutch Trial Register (NTR6759) on October 16, 2017.

Figure 1. Overall study design. T0=baseline; T1=during the intervention after 5 weeks; T2=during the intervention after 10 weeks; T3=at 1 to 4 weeks postintervention; T4=at 6 months follow-up; T5=at 12 months follow-up.



Participants' Eligibility

In total, 70 clinically depressed adolescents referred for treatment in one of nine participating mental health institutions will be asked to participate in this study, together with one of their parents. If the adolescent is 16 years or older, parents will only be approached with the adolescent's permission. Inclusion criteria for the adolescents are (1) having a clinical diagnosis of a depressive disorder, (2) aged between 12 and 21 years, and (3) referred to one of the participating mental health institutions. Exclusion criteria are (1) acute risk of suicide, (2) drug abuse (as primary diagnosis), (3) pervasive developmental disorder (as primary diagnosis), (4) bipolar disorder (as primary diagnosis), (5) day care or admission to the clinical setting, and (6) insufficient knowledge of the Dutch language. If participants

use medication, the dosage will be kept constant during the intervention.

Recruitment

Adolescents with a depressive disorder referred for treatment in psychiatric care and their parents will be informed about the study and asked to participate. Researchers will obtain written informed consent from adolescents, and parents when adolescents are younger than 16 years, before enrolling participants in this study. Additional written informed consent will be obtained from parents when they participate in the study. All adolescents meeting the eligibility criteria and willing to participate will be assigned to the D(o)epression Blended intervention.

Sample Size

The sample size (N=70) is equal to the sample size of the RCT that was already conducted in which D(o)epression face-to-face was compared with TAU. The data from this study will be compared with data from that RCT. The power analysis used in the previously conducted RCT was based on the difference between CBT and TAU at posttreatment. A meta-analysis on the effectiveness of CBT showed an effect size of 0.53 for CBT when delivered face-to-face [7]. Based on a meta-analysis on online interventions for depression (among which preventive interventions), the effect size was 0.76 [14]. Based on the literature, we assume that the effect size of blended CBT is equal to face-to-face CBT. We hypothesize that D(o)epression Blended is more effective than TAU. Furthermore, we will exploratively compare D(o)epression Blended to D(o)epression face-to-face. To detect the difference in depression diagnoses between the conditions of the previous study comparing blended CBT with TAU and this study, assuming alpha=.05 with a power of (1-β)=0.80 and dropout of 20% (power calculations in Stata), 70 adolescents will be included in this study.

Intervention

D(o)epression Blended [22] is an adaptation of the Dutch D(o)epression face-to-face program [24]. D(o)epression face-to-face is an individual CBT program based on the evidence-based treatment program Coping with Depression course for Adolescents [24]. All 15 sessions of the original D(o)epression face-to-face protocol were adapted for use in an online environment in four modules. Major adaptations included a shortening of the wording, more use of attractive visuals, and the possibility to interact online with the therapist. The online program can be combined with a minimum of 5 and maximum of 15 face-to-face sessions. The face-to-face sessions last 45 minutes each, and the adolescent and the therapist are present. Face-to-face sessions are scheduled when the adolescent starts with a new online module and at the end of the treatment, as is advised in the manual. More face-to-face sessions can be added when the therapist considers this helpful or necessary, with a maximum of 15. Additionally, there is unlimited contact between the adolescent and therapist through a chat function within the program. During the face-to-face contacts, online modules are introduced, the therapist invests in the therapeutic relationship, exercises are practiced, and suicide risk is examined. There are also two face-to-face contacts with the parents (when parents are involved): after 3 weeks and after the start of the fourth module. Parents receive psychoeducation, information about CBT, and suggestions on how parents can contribute to the treatment. All CBT therapists who will offer the D(o)epression Blended as treatment were trained by a registered clinical psychologist in how to provide blended treatment and in working with this specific blended treatment protocol in a 1-day training session.

The content of D(o)epression Blended is the same as that of the face-to-face intervention and consists of the following components: psychoeducation, setting realistic goals, self-monitoring, activation, improvement of social and communication skills, relaxation skills, cognitive restructuring, role play, problem-solving skills, and relapse prevention [25]. These components are divided into four online modules, which are offered sequentially and are called Start, Do, Think, and Future. The monitoring of mood and activities is completely online. The exercises are introduced during the face-to-face contacts and are practiced online and at home, which increases the generalizability to real-life situations. The therapist receives automatically generated prompts when the adolescent has completed a task and can view the content of the task. The online environment offers convenience, autonomy, and flexibility because adolescents can tailor their treatment preferences, such as pace, frequency, and location. This means that blended treatment is vastly different from regular treatment and allows for tailoring of the treatment to the preferences of each individual.

The control condition is TAU, which consists of a broad range of different treatments. Mental health institutions offer interpersonal therapy, family therapy, parent counseling, medication, mindfulness training, ACT (acceptance commitment therapy), psychodynamic therapy (short duration), (nondirective) counseling, creative therapy, and running therapy. For research purposes, CBT is not allowed within TAU.

Study Outcome Measures

For an elaborate overview of study variables, see Table 1.

Table 1. Overview of study variables.

Type of variable and concept	Instrument	Source			Assessment					
		Adolescent	Parent	Therapist	T0[a]	T1[b]	T2[c]	T3[d]	T4[e]	T5[f]
Primary outcome										
Depression diagnosis	Kiddie Schedule for Affective Disorders and Schizophrenia	x	x		x			x	x	x
Secondary outcomes										
Depression symptoms	Child Depression Inventory 2	x	x		x	x	x	x	x	x
Depression severity	K-SADS	x	x		x			x	x	x
Depression severity	Clinical Global Impression-Severity			x	x	x	x	x		
Depression improvement	Clinical Global Impression-Improvement			x		x	x	x		
Global functioning	Children Global Assessment Scale			x	x	x	x	x		
Suicide risk taxation	Suicide Risk Taxation	x			x			x	x	x
Comorbidity	Youth Self-Report scale/ Child Behavior Check List	x	x		x			x	x	x
Cost-effectiveness										
Quality-adjusted life-years	EuroQol Questionnaire (EQ-5D-Y)	x	x		x	x	x	x	x	x
Costs	Cost diary		x		x			x	x	x
Moderators										
Gender, age, ethnicity, education, income	Demographic Characteristics	x	x		x					
School or work	School Questionnaire	x			x			x	x	x
Alcohol and drugs	Alcohol and Drugs	x			x			x	x	x
Life events	Life Event Scale	x	x		x			x	x	x
Degree of conflicts	Network of Relationships Inventory	x	x		x			x	x	x
Parental depression	Beck Depression Inventory		x		x			x	x	x
Parental psychopathology	Adult Self-Report		x		x			x	x	x
Mediators										
Negative automatic thoughts	Cognitive Negative Cognitive Error Questionnaire	x			x	x	x	x		
Cognitive emotion regulation	Cognitive Emotion Regulation Questionnaire	x			x	x	x	x		
Attribution style	Children's Attributional Style Questionnaire	x			x	x	x	x		
Treatment characteristics										
Gender, age, experience, specialization of therapist	Therapy Procedure Checklist			x	x					
Expectancy of treatment	Parent Expectancies for Therapy Scale	x	x		x					
Previous treatments	Vragenlijst Eerdere Hulp en Interventies [History of Treatments]	x	x		x					
Satisfaction treatment	Service Satisfaction Scale	x	x					x		

Type of variable and concept	Instrument	Source			Assessment					
		Adolescent	Parent	Therapist	T0[a]	T1[b]	T2[c]	T3[d]	T4[e]	T5[f]
Therapeutic alliance	Therapeutic Alliance Scale for Children	x		x		x	x	x		
Cooperation with treatment	Cooperation With Treatment scale			x		x	x	x		
Therapy questions	Therapy Questions			x		x	x	x		
Treatment integrity	Observation			x				x		

[a]T0=baseline.

[b]T1=during the intervention after 5 weeks.

[c]T2=during the intervention after 10 weeks.

[d]T3=at 1 to 4 weeks postintervention.

[e]T4=at 6 months follow-up.

[f]T5=at 12 months follow-up.

Primary Outcome Measure

Presence of the diagnosis of depression will be measured by the Present and Lifetime version of KSADS (K-SADS-PL) [26,27]. This widely used semistructured diagnostic interview assesses a wide range of diagnoses (present and lifetime), including their severity, taking into account the view of the adolescent and the parent, and will be conducted by a trained independent research assistant. Concurrent validity of the K-SADS-PL is supported; interrater agreement is high (93%-100%), and test-retest reliability is excellent for present and lifetime diagnoses of major depression [26].

Secondary Outcome Measures

Depressive symptoms will be measured with the Dutch version of the self-report measure Child Depression Inventory 2 [28,29], and with the Child Depression Inventory 2 parent version [28] rated by the parent. The severity of the depression will be assessed using the K-SADS-PL [26]. Severity of depression will also be assessed with the Clinical Global Impression-Severity scale [30], and improvement of depression will be assessed with the Clinical Global Impression-Improvement scale [30], both rated by the therapist.

Global functioning of the adolescent will be assessed with the therapist-rated Children Global Assessment Scale [31,32]. Suicide risk will be assessed with the K-SADS-PL [26], as well as with a self-report questionnaire Suicide Risk Taxation, which focuses on the frequency of suicidal thoughts, wishes, plans, and actions over the past 2 weeks. Comorbidity and psychopathology will be assessed with the K-SADS-PL [26], and additionally with the Youth Self-Report scale [33,34], rated by adolescents, and with the Child Behavior Check List for parents [33,34].

Cost-Effectiveness Measures

Health-related quality of life will be measured with the Dutch version of the EuroQol Questionnaire (EQ-5D-Y) [35] and with the parent-rated EuroQol Questionnaire (EQ-5D proxy version) [35], which will be used to calculate quality-adjusted life-years.

The economic evaluation will be performed by registration of health care usage and costs in a cost questionnaire with a recall period of 3 months, which will be filled out by parents (which is identical to the one used in the previous RCT). Health care usage and registered costs that will be assessed are direct health care costs (eg, costs of psychologist, general practitioner, online treatment program, and medication), direct non-health care costs (eg, informal care), indirect costs (eg, monetary value of production losses caused by absence and reduced productivity and school), and out-of-pocket costs (eg, own contribution and transport costs). Costs will be calculated from a mental health care view and a societal view. The units of health care usage (eg, contact with the general practitioner, a session with a psychologist, costs of the online program) will be multiplied by the standard cost price obtained from the Dutch costing manual [36].

Moderators

Demographic information about the adolescents and parents will be assessed at baseline. Alcohol and drug use of the adolescents will be registered. Life events (such as bereavement, maltreatment, and suicide attempts), the date of occurrence, and their impact on the adolescent's well-being will be registered with the Life Event Scale [37] by the adolescent and parent. The Network of Relationships Inventory will be filled in by both adolescents and parents to measure the degree of conflicts, such as quarrels, irritations, and antagonism, in the child-parent relationship [38]. Depressive symptoms in parents will be assessed with the Dutch version of the Beck Depression Inventory, second edition [39]. Parental psychopathology will be assessed with the Adult Self-Report [40].

Mediators

Negative cognitive errors will be measured with the Negative Cognitive Error Questionnaire [41], which consists of the subscales underestimation of the ability to cope, personalizing without mind reading, selective abstraction, overgeneralizing, and mind reading. Cognitive emotion regulation will be assessed with the Cognitive Emotion Regulation Questionnaire [42] consisting of several strategies as a response to experiencing stressful events, namely self-blame, other blame, rumination, catastrophizing, positive refocusing, planning, positive reappraisal, putting into perspective, and acceptance. Attributional style will be measured with the self-report

Children's Attributional Style Questionnaire [43], which contains three dimensions of attribution, namely internal-external, stable-unstable, and global-specific.

Treatment Characteristics

At baseline, demographic information and information about education and experience of therapists will be assessed. Treatment expectancy will be measured with the Parent Expectancies for Therapy Scale [44], which will also be rated by adolescents in a revised version. Previous treatments for the adolescents' depression, such as CBT, pharmacotherapy, self-help treatments, or alternative therapies, will also be reported by the adolescents and parents with the inventory of History of Treatments [45]. Adolescents' and parents' satisfaction with treatment will be assessed with the Service Satisfaction Scale [46]. Therapeutic alliance will be reported by the adolescent and therapist using the Therapeutic Alliance Scale for Children [47]. The degree of cooperation with treatment, as observed by the therapist, will be measured with the Cooperation With Treatment scale [48]. The content of treatment will be assessed with some questions on the procedure during the therapy, such as techniques used and amount of contact through email and chat. Treatment integrity will be checked by recording two randomly chosen sessions per patient that will be observed and rated by trained psychologists. Ratings will be based on the quality of the therapist (eg, empathy, motivating patient), content of treatment (eg, following protocol, attaining goals), and structure of the session (eg, setting agenda, following time schedule). Items will be rated on a scale from 0 to 3, in which 0=absent, 1=minimal, 2=largely, and 3=maximal. A mean score for treatment integrity will be calculated.

Analyses

Intention-to-treat (imputed data) analyses and completer-only analyses will be conducted. Results will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement [49].

Preliminary Analyses

Possible baseline differences in demographic and diagnostic characteristics between the three conditions—(1) D(o)epression Blended condition, (2) D(o)epression face-to-face condition, and (3) TAU condition (the latter two conditions from the RCT, which has already been conducted)—will be checked by means of ANOVA, MANOVA, and chi-square analyses. If these variables show differences between the conditions, they will be entered as covariates in all models and regression models to test the effectiveness of the intervention.

Analysis of Primary Outcome

The primary outcome measure (ie, presence of depression diagnosis) is dichotomous and will be tested with logistic regression analyses comparing the percentage of depressive disorders in the D(o)epression Blended condition in this study to the percentage of depressive disorders in the D(o)epression face-to-face condition and the TAU condition from the previous RCT.

Analysis of Secondary Outcomes

The intervention impact on the secondary outcomes (depression symptoms, depression severity, depression improvement, quality of life, suicide risk, comorbidity) will be evaluated using linear mixed modeling with the baseline level of the concerning variable as the covariate.

Cost-Effectiveness Analyses

A cost-effectiveness analysis will be conducted by comparing the costs and effects of the D(o)epression Blended condition in this study to the costs and effects and effects of D(o)epression face-to-face and TAU. The economic evaluation will be executed in accordance with the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) Statement [50,51], which has been successfully executed previously in an economic evaluation of treatment of anxiety disorders in children [52]. The costs of blended CBT versus face-to-face CBT and TAU will be expressed in (1) incremental costs per adolescent with a depression in full remission (based on the K-SADS-PL) and (2) incremental costs per quality-adjusted life year (based on the EuroQol). To gain insight into the uncertainty surrounding subtotal and total costs, and due to highly skewed cost distributions, bootstrap simulations (1000 replications) will be conducted. Bootstrap simulations will be conducted to quantify the uncertainty around the incremental cost-effectiveness ratio [53], yielding information about the joint distribution of cost and effect differences. The bootstrapped cost-effectiveness ratios will be subsequently plotted in a cost-effectiveness plane. The bootstrapped incremental cost-effectiveness ratios will also be depicted in a cost-effectiveness acceptability curve showing the probability that a condition is cost-effective using a range of ceiling ratios. Also, sensitivity analyses will be performed to test the robustness of the results. The cost-effectiveness analyses will be done separately from a mental health perspective and a societal perspective over a period of 6 months and 1 year.

Analyses of Moderators

We will conduct a series of a priori planned moderator analyses to see if the intervention effect is moderated by the following moderators: adolescent characteristics (age, gender, ethnicity, family income), alcohol and drug use, life events, degree of conflicts, parental depression, and parental psychopathology.

Analyses of Mediator

Determining possible mediators that influence the effect of the intervention helps to identify the working mechanisms of the blended intervention. More specifically, we will test if the intervention effect on the presence of a depression diagnosis is mediated by changes in negative cognition, cognitive emotion regulation, and attributional style. The mediation analyses will be performed in Mplus [54], where indirect effects will be tested with bootstrap methods.

Other Analyses

We will also conduct analyses to see whether the feasibility of D(o)epression Blended differs from face-to-face CBT and TAU on treatment expectancy, previous treatments, satisfaction with treatment, cooperation with treatment, relationship with the therapist, treatment integrity, and dropout rate, and whether

these factors are related to the implementation and execution of the treatment program.

Results

Overview

The primary outcome is the presence of a depression diagnosis at 12-month follow-up. Several secondary outcomes will be measured, such as depressive symptoms, quality of life, and suicide risk. Costs and effects in both conditions will be compared to analyze cost-effectiveness. Further, moderating (age, gender, alcohol and drug use, parental depression, and other psychopathology) and mediating (negative automatic thoughts, cognitive emotion regulation, attributional style) effects will be tested. Also, treatment characteristics will be studied, such as characteristics of the therapists, treatment expectancy, and therapeutic alliance. The dropout rate and treatment characteristics will be measured to study the feasibility of blended CBT.

Ethics Approval and Consent to Participate

The study will be conducted according to the principles of the World Medical Assembly Declaration of Helsinki (2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (in Dutch: WMO) and other guidelines, regulations, and acts. Ethical approval has been obtained after extensive peer review by the medical ethics committee University Medical Centre Utrecht, The Netherlands (NL61804.041.17). The study is registered in the Dutch Trial Register (Trial ID: NTR6759). The study results will be reported in accordance with the CONSORT 2010 statement for reporting randomized trials [49]. Written informed consent to participate in the study will be obtained from adolescents and parents.

Funding Status

This research was funded in December 2016 by the Dutch Organization for Health Research and Development ZonMW (grant number 70-72900-98-16144).

Recruitment

The trial began recruiting participants in November 2017, and end of study enrollment was March 2019. At this time, 42 children have been recruited.

Trial Status

We are in the process of conducting the 6- and 12-month follow-up assessments. The first results are expected to be submitted for publication in 2020.

Datasets

The datasets used and/or analyzed during this study will be available from the corresponding author on reasonable request.

Discussion

Summary

This study protocol describes a pragmatic quasi-experimental controlled trial investigating the effectiveness and cost-effectiveness of a blended CBT treatment protocol in clinically depressed adolescents. Results of D(o)epression Blended will be compared with D(o)epression face-to-face and TAU. Data from the latter two conditions already have been collected in a previous study comparing CBT with TAU using an RCT design [9,10]. Testing the effectiveness of blended treatment is in accordance with the suggestions made by Calear and Christensen [55] and Richardson et al [56] to compare a blended treatment, such as blended CBT, to other active interventions, such as face-to-face CBT and TAU. Furthermore, we will examine the role of several moderators (comorbidity, depression severity, age, ethnicity, gender, family income, parental psychopathology) and mediators (negative automatic thoughts, cognitive emotion regulation, attributional style) to study who the intervention is effective for and how the intervention works. In this way, the study responds to unanswered questions about the moderators and mediators of blended interventions [6,57]. In addition, important factors in blended interventions, such as the dropout rate, feasibility, treatment expectancy, satisfaction with treatment, cooperation with treatment, relationship with the therapist, and treatment integrity will be studied.

Strengths and Limitations

One of the strengths of this study is that it is carried out in mental health institutions and that the targeted population of this study consists of adolescents referred for treatment of their depressive disorder. Participants were not recruited for treatment for the purpose of this study. This means that conclusions from the results of this research can be generalized to real-life mental health care. Additionally, the study will be conducted in several mental health care centers in the Netherlands. Therefore, our findings will not be based on the results of only one mental health institution, which adds to the generalizability of the results. Another strength is that we will compare a blended CBT treatment protocol to active treatment conditions: face-to-face CBT and TAU. Moreover, assessments will be based on multiple informants (ie, adolescents, parents, and therapists).

This innovative blended treatment has considerable potential. It incorporates the positive characteristics of online interventions, such as high accessibility, and the potential to be easily tailored to the daily lives of adolescents. To our knowledge, this is the first study on the effectiveness of blended CBT treatment of depressive disorders in adolescents. Therefore, we can uniquely contribute to the crucial evidence-based improvement of treatment protocols in mental health care.

A limitation is that the study is not designed as an RCT. In this study, we will recruit participants for the blended CBT condition only. The results of these participants will be compared with participants recruited in the earlier conducted RCT, in which face-to-face CBT was compared to TAU. Since there is no randomization in the current trial, it cannot be ruled out that there are slight differences in the participants, therapists, or societal context. We will try to keep this potential threat to internal validity as low as possible by working with the same inclusion and exclusion criteria for participants and with the same or similar mental health institutions. However, this pragmatic quasi-experimental design will deliver preliminary

evidence and very relevant information on the effectiveness and cost-effectiveness of blended CBT in routine care.

Implications for Practice

If the blended CBT program D(o)epression Blended proves to be effective and cost-effective in treating depressive disorders in adolescents in mental health care, then D(o)epression Blended could be widely implemented in mental health institutions. This could expand the treatment choices of depressive disorders in adolescents and improve the potential to tailor and personalize the treatment.

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Authors' Contributions

SR was responsible for data collection and writing the manuscript. SR, YS, and DB were responsible for data analysis and for reporting the study results. MD will be involved in the data analysis. YS, HR, MD, MN, CD, DC, and DB were the grant applicants, and they read the manuscript and provided suggestions for improvement. All authors have approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Funder peer-review report (ZonMw).
[PDF File (Adobe PDF File)535 KB - resprot_v8i10e13434_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia
K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version
RCT: randomized controlled trial
TAU: treatment as usual

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Protocol

Acceptability and Feasibility of a Telehealth Intervention for Sexually Transmitted Infection Testing Among Male Couples: Protocol for a Pilot Study

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Abstract

Background: Gay, bisexual, and other men who have sex with men (MSM) are at elevated risk for acquiring sexually transmitted infections (STIs) in the United States, especially chlamydia and gonorrhea. While research has indicated main partners over casual partners may play a central role in STI risk, the frequency of STI screening among MSM couples is particularly low. Self-sample collection for chlamydia and gonorrhea screening has been shown to be highly accurate, and at-home STI testing has been shown to be highly acceptable among diverse populations. However, there is little research exploring the feasibility and acceptability of at-home chlamydia and gonorrhea screening among MSM couples. Our pilot study aims to help evaluate the viability of this screening modality as an intervention tool for MSM couples

Objective: The objective of this study was to assess the feasibility and acceptability of an at-home chlamydia and gonorrhea sample collection and remote lab testing program among a sample of 50 MSM couples living in the United States.

Methods: This pilot study enrolled 50 MSM couples, ranging from 18-40 years old and living in the United States, who participated in a larger at-home HIV testing randomized controlled trial. Participating couples completed a pretest instructional video call and then had the option of completing at-home sample collection across three bodily sites (rectal swab, pharyngeal swab, and urine sample) for remote chlamydia and gonorrhea lab testing. For participants who completed any sample collection, they received their results via a posttest video call. All participants completed an online survey examining satisfaction and acceptability of the home testing process, experience with logistics, willingness to test at home in the future, recent sexual risk behavior, STI testing history, and linkage to care. A subset of 10 couples completed an in-depth interview about their attitudes towards the sample collection process, different decisions they made while collecting their samples, and their experience accessing treatment (for those who received a positive result).

Results: Recruitment began in September 2017, and as of March 2019 a total of 50 couples have been enrolled. Overall, 49/50 couples have returned their samples and completed the posttest delivery call, and 10 in-depth interviews have been completed and transcribed.

Conclusions: Screening MSM couples at home for chlamydia and gonorrhea and providing video-facilitated results delivery may offer a tailored approach to address the increasing prevalence of these STIs. By collecting data on how MSM couples experience at-home STI screening, this project will provide valuable insight into the utility of such a service delivery program to public health interventionists and researchers alike.

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sexually transmitted diseases; telemedicine; sexual and gender minorities

Introduction

In the United States, gay, bisexual, and other men who have sex with men (MSM) are at elevated risk for acquiring sexually transmitted infections (STIs) relative to heterosexual men and women [1-4]. Although women in the United States experience a higher burden of chlamydia than men, increased screening over time has shown the rate of infection among men increased by almost 40% between 2013-2017, a rise primarily attributed to rising incidents of infections among MSM [5]. Across 30 STI clinics within 10 US STI surveillance districts, the median site-specific chlamydia prevalence for MSM was 4.8% for urethral specimens, and 16.8% for rectal specimens in 2017 [5]. Among those same clinics, the median site-specific gonorrhea prevalence for MSM was 8.5% for urethral specimens, 14.7% for rectal specimens, and 13.4% for pharyngeal specimens in 2017 [5]. This is particularly troubling given the appearance of increasingly prevalent strains of treatment-resistant gonorrhea. Using gonorrhea case data derived from 27 US state or city health departments from 2011-2016, the Gonococcal Isolate Surveillance Project found that isolates from MSM were significantly more likely to show signs of antimicrobial resistance than specimens from heterosexual men [5]. With such high rates of chlamydia and treatment-resistant gonorrhea, improving routine screening among this population has become a key public health priority.

Counter to past conceptualizations that posited casual sex partners were central to STI risk, recent modeling analyses indicate that between one- and two-thirds of new HIV infections among MSM are attributable to main sexual partners [6,7]. Although these findings are specific to HIV, they remain relevant to chlamydia and gonorrhea due to the high comorbidity of these STIs and their similar transmission pathways [8]. Infections derived from main partners are driven by MSM being more likely to have anal sex, being less likely to use condoms with their main partners compared to casual partners [7,9-11], and tending to have more overall sex acts per year with main partners [7]. To compound this elevated risk context, MSM with main partners report lower levels of routine HIV testing than single MSM [12,13]. While data on the prevalence of STI testing among MSM couples is limited, Mitchell and Petroll found that, on average among 361 MSM couples in the United States at the time of the survey, they reported testing for other STIs, besides HIV, about 19.1 months ago [14]. These high rates of HIV transmission, sexual risk behavior, and low frequency of HIV or STI screening suggest that MSM couples may be at particular risk for undiagnosed STIs such as chlamydia and gonorrhea.

To curb the STI epidemic in the United States, experts have increasingly called for more efficient deployment of self-testing modalities among populations at risk [15]. Calls to increase self-testing are partially due to home testing technology demonstrating similar effectiveness in identifying and treating cases of STIs relative to clinic-based testing strategies. A Cochrane review of 10 clinical trials that compared home-based chlamydia or gonorrhea testing to clinic-based testing found that home-based testing achieved higher screening uptake among participants and resulted in similar levels of treatment [16]. Another meta-analysis of self-collected chlamydia or gonorrhea samples versus clinician-collected samples found similarly high sensitivity and specificity of self-collected swabs and urine samples [17]. Beyond effectiveness, at-home STI testing is considered acceptable across diverse populations. A systematic review of patient experiences when self-testing for curable STIs found, across 36 studies, that 85% of participants reported self-sampling as being acceptable, and across 28 studies, 88% of participants reported it was easy to use while only 13% reported any pain or discomfort [18].

Although at-home STI testing has been successfully administered to single MSM [19-21], to our knowledge no such data exists on the acceptability and feasibility of at-home STI testing among MSM couples. Across 15 couple-based interventions that focused on at least one HIV prevention outcome (ie, sex or drug use behavior, HIV or STI testing, HIV treatment uptake, and medication adherence), a recent meta-analysis found that these dyadic interventions produced significantly higher changes in sexual risk, HIV testing, and Nevirapine uptake relative to individual intervention comparison groups [22]. This evidence suggests that interventions designed for couples operate on behavioral change outcomes in significantly unique ways relative to interventions designed for individuals. Therefore, individual MSM data on the acceptability and feasibility of an intervention, such as STI screening, may not be translatable to how MSM couples would experience the same intervention as a dyad. Since there were only two studies in the meta-analysis examining STI testing (both of which were conducted among heterosexual couples), there was also insufficient evidence to examine how couple level interventions may produce different effects in STI screening compared to individualistic approaches [22]. The dearth of couples' STI testing studies signals the need for more research in this area, particularly among MSM couples. This study begins to address this gap by developing and piloting an at-home STI testing protocol specifically designed for MSM couples.

The home environment may be uniquely suited to reach at-risk MSM couples for STI screening. Piloting research on how male couples experience at-home sample collection and remote lab testing may offer critical data in evaluating the viability of this screening modality as an intervention tool. This paper describes the protocol for a pilot study of at-home chlamydia and gonorrhea testing and remote video call results delivery for MSM couples living in the United States and aged between 18-40 years old. The procedures described below have been reviewed and approved by the Institutional Review Board at the University of Michigan in Ann Arbor (HUM00131366) and have been deemed to pose no more than minimal risk to study participants.

Methods

Study Overview

The Project Nexus STI At-home Testing Pilot Study is an exploratory project of 50 male same-sex couples, aged 18 to 40 years old and living in the United States, who recently completed a larger clinical trial of remote couples' HIV testing and counseling via remote video call [23]. The age range restriction was developed in order to better align with the younger trend of chlamydia and gonorrhea diagnoses in the MSM community [5]. To be eligible, couples needed to be HIV-negative by the end of the original trial, report still being in a relationship with the partner they started the original study with, and both had to express their interest to participate to study staff individually. Eligible couples scheduled an introductory Health Insurance Portability and Accountability Act (HIPAA)-compliant video call with study staff, who reviewed the informed consent document, obtained their verbal consent to participate, and demonstrated how to use the at-home chlamydia and gonorrhea sample collection kit materials. After completing the call, each partner was sent a discreet box containing instructions and supplies to self-collect a pharyngeal swab, a rectal swab, and a urine sample. For those who decided to collect and return their samples, they were screened for chlamydia and gonorrhea. Testing across these three sites is of importance because, until recently, testing protocols for gonorrhea and chlamydia among MSM mainly focused on detecting urethral infections, which are more likely to be symptomatic than pharyngeal and rectal infections [24]. Once study staff received each partner's multi-site test results from the processing laboratory, the couple scheduled another video call with study staff to go over their test results and receive tailored risk reduction counseling. Upon receiving their test results via video conferencing, each partner was sent an incentivized online survey, to complete individually, that aimed to assess recent sexual risk behavior, STI testing history outside of the study, and acceptability of the at-home testing procedures. Lastly, we conducted 10 in-depth interviews with 10 couples to explore any potential barriers or facilitators to their experience collecting their samples at home and receiving their results through video conferencing.

Participant Recruitment

The STI at-home testing pilot recruited and enrolled 50 male same-sex couples, aged 18-40 years old, who were sero-concordant, HIV-negative, and resided in the United States. Participants were recruited from past participants who completed the original at-home HIV testing study and who, by the last follow-up survey, reported being HIV-negative and were still together with their romantic partner. The original trial recruited male couples across the United States via online advertisements placed on Facebook, Instagram, Scruff, Grindr, and Poz Magazine, and through email referrals sent to past respondents of the Emory-based American Men's Internet Survey. Study staff reviewed participant data in the original study to compile a list of eligible couples to invite to participate. Couples were contacted regarding their eligibility via email, phone call, or text message, depending on their contact preferences using standardized scripts. Both partners had to individually express interest in the study before continuing forward.

Study Procedures

Pretest Instructional Call

If both partners of an eligible couple communicated interest in participating in the pilot project individually, study staff scheduled a preliminary video call with the couple that lasted approximately 15 minutes. Before the scheduled call, the eligible couple was sent the informed consent document for their review. This video call was conducted using a HIPAA-compliant video call service called VSee. During the preliminary video call, study staff went over the informed consent form, clarified any questions the couple had, and asked if they chose to provide consent to join the pilot project. While reviewing the consent form, study staff also discussed the risk of potentially feeling coerced into participation by their partner. Anyone experiencing coercion from their partner was encouraged to contact study staff privately and those couples would be independently offered the at-home testing kits as well as a list of local STI screening centers if they preferred alternate mode of testing, but they would not be included in the study sample. Men who did not consent, or whose partner did not consent, were thanked for their time but did not move forward in the study. If both partners agreed, the staff member then went over the contents of the three-site, at-home gonorrhea and chlamydia test kit, and explained how they would use each element. The instructions included going over the urine sampling procedure, the rectal swab sampling method, and the pharyngeal swab process. Study staff screen-shared images of the appropriate sampling procedure and physically demonstrated with the self-collection supplies the effective techniques following laboratory guidelines. Study staff also went over frequently asked questions tailored to the behaviors of MSM, such as avoiding rectal douching before collecting the rectal sample. After the couple had become familiar with the test kit and communicated understanding about how they would collect their test samples, study staff then confirmed the shipping address where they would like to have their test kit sent. Afterward, study staff conducting the call filled out a case report form as a fidelity measure documenting the couples' verbal consent and the instructions provided.

At-Home Sample Collection

Overview

Once study staff confirmed a couple's shipping address, they sent one package containing two sample collection kits, one for each partner. The box was packaged discreetly, with no identifiable information regarding the study on the exterior. Each sample collection kit had the corresponding partner's first name labeled on the exterior to indicate which kit was assigned to them. All test sample materials returned for lab processing were only identified by a randomly generated number separate from their study identifier to blind the processing laboratory to the identities of participants. Package instructions not only detailed the sample collection procedures covered in the pretest video call but urged participants to return their test samples as soon as possible. Couples were informed they could either collect the samples separately or together, depending on their preference. Couples could also choose to return some, or none of their samples for chlamydia and gonorrhea testing. The package instructions included detailed written descriptions of

self-collection techniques for their pharyngeal, urine, and rectal samples, alongside color illustrations for further guidance.

Pharyngeal Swab Self-Collection

Each partner was instructed to wash their hands thoroughly prior to collection. Then, they unscrewed the top of a transport tube and opened the sterile packaging of a cotton swab stick. With the swab stick in hand, each partner swabbed the back of their throat on either side where their tonsils were located. Upon completion, they inserted the cotton swab end of the stick into the transport tube and broke off the top half, leaving the swab inside. Upon tightly screwing on the top of the transport tube and placing it into a provided biohazard bag, each partner could throw away the leftover materials.

Urine Sample Self-Collection

Each partner was instructed to wait at least one hour since they last urinated before collecting their urine sample. Once the proper amount of time had elapsed, participants again washed their hands. Then, they unscrewed the sealed lid of a 30-ounce specimen cup and collected the first initial stream of urine into the cup, filling it to a demarcated line at 5 ounces. After washing their hands again, participants extracted some of the urine using a pipette, unscrewed the lid of another transport tube, and filled the tube with urine between the minimum and maximum fields on the tube. Finally, each partner tightly screwed the top on the transport tube and inserted it into the same biohazard bag. The pipette, specimen cup, and instructions could then be thrown away in the garbage.

Rectal Swab Self-Collection

Prior to self-collection, participants needed to wash their hands a final time and then unscrew the cap of the last transport tube. Like the pharyngeal swab, they opened the sterile paper packaging to remove the cotton swab stick. Each partner then inserted the swab into his rectum an inch and a half, using provided lubricant as needed. With the swab stick inside at the right depth, they rotated the swab gently in a circular motion several times and then withdrew. Placing the cotton end of the swab into the transport tube, they broke off the stick portion, leaving the cotton end inside. As a final step, each partner screwed on the top of the tube and placed it in the biohazard bag with the rest of their samples. The remaining materials could then be thrown away.

Sample Return

With all three samples in the biohazard bag, each partner then sealed the bag and wrote in the current date on a separate lab information form. Both the biohazard bag and the completed form were inserted into a bubble wrap mailer with a prepaid FedEx return shipping label affixed to the front. While the swab and urine samples are considered stable between 35°F-86°F for up to 30 days, the return packaging materials were designed to help prevent sample degradation during transit. The return shipment type was FedEx standard overnight delivery so that the samples could arrive at the processing laboratory by the next business day and minimize exposure to unideal conditions. The biohazard bag was a ThermoSafe specimen transport bag with absorbent sheets to protect against spills, and the return shipment package was an opaque bubble wrap mailer to reduce ultraviolet exposure and physical damage during shipment. The return shipment packaging was discreet and mentioned nothing regarding the nature of the study nor any identifiable information traceable to either partner. After sealing their return shipment package, each partner was able to either schedule for FedEx to pick up the package or find a FedEx store, or drop-off box, to leave it at to be shipped. Collecting and returning specimens was not incentivized and participants could continue in the study without collecting them. All samples were sent to the Emory University Clinical Virology Laboratory to be tested using the US Food and Drug Administration approved Abbot real-time chlamydia trachomatis and Neisseria gonorrhea polymerase chain reaction assay, which detects a region of the cryptic plasmid DNA of Chlamydia trachomatis and a region of the Opa gene of Neisseria gonorrhea [25]. For chlamydia trachomatis the assay's sensitivity=92.4% and its specificity=99.2%, and for Neisseria gonorrhea the assay's sensitivity=96.9% and its specificity=99.7% [25]. Results from the processing lab were shared with study staff through a HIPAA-compliant cloud storage service called Box. Only institutional review board–approved study staff were able to link test results to any participant via the randomly assigned sample identifier and the study identifier.

Posttest Results Delivery Call

Once study staff received both partners' chlamydia and gonorrhea test results, they contacted the couple to schedule another video call via VSee that would last approximately 20 minutes. The purpose of the call was to deliver each partner's test results, provide linkage to care if needed, and create a prevention plan tailored to the couple's sexual behavior and risk. Study staff who facilitated these calls were certified in HIV counseling, testing, and referral, and trained in couples' HIV testing and counseling. During the call, both partners needed to verbally consent to receive their test results together or opt in to receive their results separately over two video calls scheduled at different times. Both partners also needed to agree to mutual confidentiality and disclosure (ie, agreeing they would not divulge their partner's test result to someone outside of their relationship without their partner's prior consent). They could also refuse to receive their results entirely and continue with the rest of the study. If both partners consented and agreed to the confidentiality and disclosure stipulation, the study team member would start by reiterating what samples were collected and the chlamydia and gonorrhea results that were possible (eg, having a positive result at one area of the body but not anywhere else). Afterward, study staff screen shared a document containing each partner's test results across each of the three bodily sites and discussed each one. Upon receiving their results, study staff facilitated a conversation around sexual risk behavior, STI prevention, and screening. After completion, study staff conducting the call filled out a case report form as a fidelity measure, documenting the couples' consent, results, and prevention plan.

When participants received a positive chlamydia or gonorrhea result, study staff sent them an email of local STI treatment clinic referrals within 48 hours of the result delivery video call. During the call, study staff requested the location where the participants would like to receive STI clinic information from

and discussed the importance of getting treatment. Negative partners of an individual with a positive test result were also encouraged to screen again and were given the option of receiving local STI screening sites in their area. Resources were compiled using the Centers for Disease Control (CDC) testing site locator and the United Way 211 organization database. Study staff followed up with any individual who received a positive test result 14 days after the result delivery call to assess receipt of treatment over the phone and help troubleshoot any issues encountered. A case report form was filled out after this follow-up call to document treatment status or reasons for not seeking treatment. Participants who received an invalid chlamydia or gonorrhea result for any one, or all, their samples were offered a list of STI testing sites in a location of their choice, but they were not provided another at-home chlamydia and gonorrhea sample collection kit through the study.

Acceptability Survey

After receiving their results or refusing to take part in the at-home testing portion of the study, participants were sent an email with a hyperlink to a secure online survey programmed in Qualtrics (Qualtrics XM, Seattle). The survey included questions regarding satisfaction and acceptability of the home testing process, experience with logistics (ie, the clarity of the pretest instructions), willingness to test at home in the future, recent sexual risk behavior, STI testing history, and linkage to care. Satisfaction, acceptability, and willingness measures were adapted from the Client Satisfaction Questionnaire [26] alongside those derived from other studies of at-home HIV testing trials [23,27]. Sexual behavior was assessed by using measures adapted from the National HIV Behavioral Surveillance inventory [28]. Participants were asked to estimate the number of anal sex encounters they had with their primary partner and any outside partners, the number of those encounters where condoms were used, and the number of times where they were the insertive or receptive sexual partner. STI screening questions and linkage to care items were based on the CDC's STI screening and treatment guidelines for chlamydia and gonorrhea [29]. Participants were sent a reminder to complete the survey via their preferred contact method two weeks after receiving it, and again four weeks later. After those two reminders they were not contacted again.

In-Depth Interview

A subset of 10 couples who completed the testing portion of the study were invited via email to participate in an in-depth interview conducted remotely via VSee video call that lasted approximately 30 minutes. Study team members recruited participants through purposive sampling to help obtain interviews with five couples where at least one partner received a positive test result and five couples where both partners received negative results, as well as to have at least 10/20 participants identify as nonwhite. During the interview, couples were asked about their attitudes towards the sample collection process, different decisions they made while collecting their samples (ie, collecting their samples together or separately), and their experience accessing treatment (for those who received a positive result). Verbal consent to have the audio of the interview recorded and transcribed for future analysis was required from both partners for the interview to proceed. Upon receiving an initial invitation to participate in the interview via their preferred contact method, unresponsive couples were invited once more two weeks later. After those two invitations they were not contacted again.

Analysis

Descriptive statistics will be used to quantify characteristics of participating couples, such as relationship status, STI testing history, and recent sexual behavior, using Stata version 14 [30]. Descriptive statistics will also be used to assess overall satisfaction and acceptability of the home sample collection procedure and delivery of results among participants. Proportions of each sample type (ie, rectal, pharyngeal, urine) returned and the adequacy of the specimen collection for chlamydia and gonorrhea testing will be calculated. Linkage to care will be analyzed through aggregated counts of follow-up interactions detailing receipt of treatment post-result delivery. Chi-square tests will be used to assess any significant differences in positive versus negative experiences of the intervention by various demographic variables (ie, race, ethnicity, age, relationship type).

In-depth interviews will be transcribed and double checked for any discrepancies with the original audio files. All identifiable information, such as names and locations, will be removed before analysis. Verified transcripts will undergo a deductive coding strategy wherein a code hierarchy of key information (ie, attitudes toward the sample collection procedure, reasons for testing together or separately, experiences with finding treatment) will be developed by the research team and used by analysts to systematically code the qualitative data [31]. Analysts will meet regularly during the coding phase to discuss and reconcile coding inconsistencies, as well as revisit the code structure for possible revision and additions if there are described experiences not captured by the original schema. After the coding phase has been completed, thematic analysis will be conducted on extracted quotes by code area to pull overarching themes across the dataset.

Incentives

All participants received a $50 Amazon electronic gift card via email for completing the acceptability survey and an additional $30 Amazon electronic gift card for completing the in-depth interview. Returning samples to be tested for chlamydia and gonorrhea or completing the post-test results delivery call were not incentivized study activities.

Results

Recruitment began in September 2017 and ended in October 2018. A total of 75 couples were screened and deemed eligible and then invited to participate in the pilot study. Nineteen couples were either uninterested or did not reply to the invitation, 5 couples reported no longer being together, and 1 couple dropped out after initial enrollment. A total of 50 couples were enrolled, with 49 returning their samples and completing the posttest delivery call. Nine individuals tested positive for chlamydia or gonorrhea, and all successfully obtained treatment at the 14-day follow-up call. Ten in-depth interviews were

completed and transcribed. Analysis of the study results is currently underway.

Discussion

The Project Nexus STI At-Home Testing Pilot Study aims to evaluate preliminary acceptability of at-home chlamydia and gonorrhea self-collection and remote, video-facilitated results delivery among MSM couples living in the United States. Being able to test and receive STI results at home with a primary partner may help reduce barriers to screening and facilitate tailored conversations around sexual health for each couple's specific circumstances. Because current CDC guidelines for expedited partner therapy (providing antibiotic treatment for chlamydia or gonorrhea to an external sexual partner who has yet to be tested) only pertain to heterosexual cases [32], having MSM couples screen together for these STIs may help ensure both partners can access treatment or retesting without solely relying on partner notification. By exploring the feasibility of at-home chlamydia and gonorrhea screening among MSM couples, our pilot may identify new avenues of research to help curb the STI epidemics among this highly affected population.

Because our pilot project derived its sample from a larger study of at-home HIV testing, the generalizability of our findings will be limited to this context. Our participants fully completed participating in a research trial with a 6-month follow-up period, so each partner's ability to coordinate with one another on study-related tasks may be systematically different than couples who did not fully complete the original study. Moreover, couples who were still in a relationship by the time they were invited to participate in the pilot study may be demographically unique from those who were no longer together by the time of invitation. During analysis, we will compare our sample to those who were uninterested in participation, and who reported no longer being together, to determine any statistically significant differences. To our knowledge, no prior research has attempted to survey how MSM couples experience at-home STI screening, and with this context we believe our research will still be able to provide a useful base for future inquiry. Additionally, by allowing couples to opt out of the STI screening portion of the study, our ability to assess the acceptability of the sample collection materials and linkage to care could have been reduced. However, we believe that providing this option offered meaningful data on the willingness and interest MSM couples may have in these services. Lastly, we recognize the possibility of conflict that may arise when couples receive sensitive STI test results together. To minimize this potential adverse implication, we allowed partners the option to receive their results individually and we monitored relationship dissolution throughout the project period. However, we did not collect data on other indicators of relationship conflict, such as intimate partner violence or interpersonal stress, so our ability to assess conflict stemming from the at-home STI testing experience is limited to reports of relationship dissolution.

Despite these limitations, screening MSM couples at-home for chlamydia and gonorrhea and providing video-facilitated results delivery may offer a tailored approach to addressing the increasing prevalence of these STIs. By collecting data on how MSM couples experience at-home STI screening, this project will provide valuable insight into the utility of such a service delivery program to public health interventionists and researchers alike.

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Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control
HIPAA: Health Insurance Portability and Accountability Act
MSM: men who have sex with men
STI: sexually transmitted infection

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Protocol

Analyzing Nursing Students' Relation to Electronic Health and Technology as Individuals and Students and in Their Future Career (the eNursEd Study): Protocol for a Longitudinal Study

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Abstract

Background: The nursing profession has undergone several changes in the past decades, and new challenges are to come in the future; patients are now cared for in their home, hospitals are more specialized, and primary care will have a key role. Health informatics is essential in all core competencies in nursing. From an educational perspective, it is of great importance that students are prepared for the new demands and needs of the patients. From a societal point of view, the society, health care included, is facing several challenges related to technological developments and digitization. Preparation for the next decade of nursing education and practice must be done, without the advantage of certainty. A training for not-yet-existing technologies where educators should not be limited by present practice paradigms is desirable. This study presents the design, method, and protocol for a study that investigates undergraduate nursing students' internet use, knowledge about electronic health (eHealth), and attitudes to technology and how experiences of eHealth are handled during the education in a multicenter study.

Objective: The primary aim of this research project is to describe the design of a longitudinal study and a qualitative substudy consisting of the following aspects that explore students' knowledge about and relation to technology and eHealth: (1) what pre-existing knowledge and interest of this area the nursing students have and (2) how (and if) is it present in their education, (3) how do the students perceive this knowledge in their future career role, and (4) to what extent is the education capable of managing this knowledge?

Methods: The study consists of two parts: a longitudinal study and a qualitative substudy. Students from the BSc in Nursing program from the Blekinge Institute of Technology, Karlskrona, Sweden, and from the Swedish Red Cross University College, Stockholm/Huddinge, Sweden, were included in this study.

Results: The study is ongoing. Data analysis is currently underway, and the first results are expected to be published in 2019.

Conclusions: This study presents the design of a longitudinal study and a qualitative substudy. The eHealth in Nursing Education eNursEd study will answer several important questions about nursing students' attitudes toward and use of information and communications technology in their private life, their education, and their emerging profession. Knowledge from this study will be used to compare different nursing programs and students' knowledge about and relation to technology and eHealth. Results will also be communicated back to nursing educators to improve the teaching of eHealth, health informatics, and technology.

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KEYWORDS

internet; nursing; eHealth; nursing student; digitization

Introduction

Background

This study presents the design, method, and protocol for a study that investigates undergraduate nursing students' internet use, knowledge about electronic health (eHealth), and attitudes to technology and how their experiences of eHealth are handled during the education in a multicenter study. The nursing profession has undergone several changes in the past decades, and new challenges are to come in the future; patients are now cared for in their home, hospitals are more specialized, and primary care will have a key role. Health informatics and all forms of eHealth are essential parts of all core competencies in nursing. In this text, we will use the broad World Health Organization (WHO) definition of eHealth, "the use of information and communication technologies (ICTs) for health" [1].

Digitization can be described as a transformation, with far-reaching consequences in the lives of individuals as well as in the functioning of the society. Like almost all sectors of society, health care systems are increasingly characterized by digitalization and relying on technical aids and tools to solve basic assignments and needs. New technology can lead to great values in the form of safer and smoother care, increased quality of life, and socioeconomic efficiency improvements. The increased digitization and development in the eHealth area enables new ways of creating knowledge and conducting care, but information about people's health is very sensitive, and incorrect handling of data can lead to serious consequences for the individual person. With the digitally available information, diseases can be prevented; medical quality and patient safety can be raised; and health care can be more efficient, coordinated, accessible, and transparent. To meet future demands, nursing students need to have knowledge about new technologies and eHealth. Therefore, there is a need for enhancing education in the field, although undergraduate students today are considered digital natives [2].

From a societal point of view, the society, health care included, is facing a number of challenges related to technological developments and digitization. Welfare technology is presented as 1 important way to meet this challenge: it can free resources, provide support to those who are in need, and decrease expenses. Furthermore, it is an important field for research, development, and innovation [3]. It is predicted that today's dominating scenarios of human interaction and communication will, in the future, be complemented by an increase in the numbers of communicating machines. It is also expected that there will be 20 billion devices or things connected to the internet by 2020 [4]. Moreover, from an educational perspective, it is very important that students are prepared for the future demands and needs of the patients. Preparation for the next decade of nursing education and practice must be done without the advantage of certainty. A training for not-yet-existing technologies where educators should not be limited by present practice paradigms is desirable [5]. An important means to achieve the digitization goal is to increase digital literacy and competence in the society as a whole [6,7].

The Global Commission on Education of Health Professionals for the 21st century describes a lack of cooperation and discontinuous care [8], which poses demand on high-quality education in the field of technology in health care [9]. It is not only in high-income countries that the technological development is increasing tremendously but also in middle- and low-income countries where technological development is galloping, and the increased number of cellphone users and internet technologies has given new possibilities to reach areas that were not reachable before and people in developing countries. In addition, the technique is cheaper, which also enhances the number of users, including the older generation with new demands and possibilities [10].

In a report by WHO [11] about eHealth and how it can be beneficial for and support universal health coverage (UHC), it is stated that training of students as professionals in eHealth and electronic learning will contribute to reaching these goals for UHC. The report also points out that different areas within eHealth are rapidly increasing. Out of 109 responding countries, the vast majority (87%) answered that there is at least one mobile health (mHealth) program in their country. For low-income countries, the percentage was 80%, and for high-income countries, the percentage was 91%. There were several programs in the pipeline, but evaluations of these projects were few. In Sweden, the Government and the Swedish Association of Local Authorities and Regions have stated a vision for eHealth in Sweden [12]:

> *In 2025, Sweden will be best in the world at using the opportunities offered by digitization and eHealth to make it easier for people to achieve good and equal health and welfare and to develop and strengthen their own resources for increased independence and participation in the life of society.*

Similar actions are taken globally; in Australia, the government of Queensland has undertaken a digital strategic vision for eHealth care including digital innovations [13], and in the European Union (EU), there are several initiatives for increasing and supporting digital transformation and digitization of health care [14]; for example, the European health telematics association, ETHEL, a platform for stakeholders that facilitates collaboration innovations and developments between health care and caregivers regarding digital health and care.

In the United States, there is an organization, the American Nursing Informatics Association (ANIA), whose goal is to improve care for patients and optimize management and communications for caregivers by delivering cost-effective, high-quality health care. In ANIA, nursing science, computer science, and information science are integrated [15]. Likewise, the Canadian Nurses Association (CNA) and the Canadian Nursing Informatics Association (CNIA) emphasize the importance of knowledge of nursing informatics within the

nursing profession. CNA and CNIA point out that to reach a person-centered care-model, digitally connected health services environments are essential tools to empower the nurses in their caregiving [16]. In South Africa, with over 88 million mobile phone subscribers [17], the government has adopted an mHealth strategy to develop the health system and to transform health service delivery within the country to improve the efficiency of health care [18].

Implications for the Nursing Profession

Health informatics is an important part in all core competencies in nursing [19]. In a survey from 21 different countries, different areas of health informatics were identified as key domains in health and nursing informatics. These were "data, information, knowledge," "information exchange and information sharing," "ethical and legal issues," "systems life cycle management," "management," and "biostatistics and medical technology" [20]. The concept of health informatics is continuously developing [21], and the increasing digitalization of health care has identified the need for both general and specific digital competence and digital literacy in the nursing profession and education [22-24]. However, nursing informatics research on education, clinical practice, administration, and theory is scarce, with the theory being the least common [25]. Digitization has developed care practices, provides opportunities for the nurse to monitor patients at home, and facilitates control of patients, medications, etc [9,26,27]. WHO [28] defines digital health as general use of ICTs for health, including both internet- and mobile-based tools or apps aimed at treating and preventing diseases or promoting health and well-being. The complex process of integration of information and communications technology (ICT) into nursing practice impacts nurses' communication and relationships in patient care as well as their working condition, professional identities, and development [29]. This has led to an increasing interest into various aspects of nurses' ICT use, such as mobile phones in different care settings [30-33], social media [34,35], electronic records [36], Web-based guidelines [37,38], patient engagement technology [39], telehealth and telenursing [40], decision support [41], patient self-management [42], cybersecurity awareness [43], and multimedia Web-based simulation for competence development [44].

The importance of a structured approach to nurses' use of eHealth has led nursing professional organizations in many countries to develop their own strategies in the area. In Sweden, the National Nursing Association (Swedish Nurses' Association) has pointed out the importance of the necessary conditions and skills that are needed for added value both for patients and professionals from eHealth [45]. The strategy describes nurses' responsibility for creating a relationship with patients and related parties based on a humanistic vision even when digital aids are used. It also highlights the importance of nurses participating to influence the development of the eHealth services nursing support.

Implications for Nursing Education

It is necessary that nursing students are prepared to enter their professional role with knowledge and skills in eHealth. How nursing education is helping (or not) in this preparation and the strategies used to achieve this goal [46] is an important focus area. The reality that meets nursing students in their daily lives, in their education [47], and in their future career role is constantly changing in terms of the infrastructure they work within and the tools at their disposal. At the same time, the basic values and assignments are essentially the same [48]. This poses new ethical questions that need to be taken in to account [49]. In a study conducted by Montagni et al [50] about patterns of digital health use among university students in France, it was found that the students were confident that mobile apps and digital health interventions will replace physical consultations if they were launched by the government. Furthermore, the study shows that there is a potential for improving health and well-being among university students by using digital health interventions as the students are already using the internet for that purpose. These findings are confirmed by Covey and Potts [51] in a recent qualitative study with focus groups that aimed to understand undergraduate students' experiences of both digital and broader health care to enable a better understanding of implications for national policy as well as for individual health care organizations. The study results also indicate that the apps need to be developed in collaboration for enhanced understanding and usefulness of the digital tools. These "digital native" students need to be convinced of the benefits of the tool before using it. In a Dutch study [52], however, this "internet-generation" nursing students were shown to not naturally have a positive view of technology-based health care provision. Although they could be seen as "digital natives," they do not naturally display a positive view of technology-based health care provision, showing that adequate technology and telehealth education is still necessary.

Moreover, a study measuring students' perceptions of the usefulness and ease of use of technology as a pedagogical tool in nursing education showed that they saw it as highly useful. In addition, use of social media in nursing education attracts interest as a learning platform [53-55] but is not seen as uncontroversial despite the potential benefits [56].

Early teaching of digital skills in undergraduate nursing students will enhance the development of digital professionalism among the students also in the health care environment [57]. These findings are essential for the implications of this study as they confirm that early digitization is important in the curriculum. This study presents the design, method, and protocol for a study that investigates undergraduate nursing students' internet use, knowledge about eHealth, and attitudes to technology and how experiences of eHealth are handled during the education in a multicenter study.

Objectives

eNursEd is a long-term research and development project aimed at describing, investigating, and analyzing nursing students' relations to eHealth and technology as individuals and students and in their future career role. eNursEd is a collaborative project between the Blekinge Institute of Technology (Blekinge Tekniska Högskola, BTH) and the Swedish Red Cross University College (SRCUC) and is ongoing from 2017 onward.

The primary aim of the research project is to learn about the students' knowledge about and relation to technology and

eHealth. The project aims to investigate what pre-existing knowledge and interest of this area the nursing students have and how (and if) it is present in their education. In addition, the project aims to investigate how they perceive this knowledge in their future career role and, in particular, to what extent the education as such is capable of managing this knowledge.

Methods

Study Design and Setting

The study consists of 2 parts: a longitudinal study and a qualitative substudy.

The primary study has a longitudinal design, and data will be collected through a questionnaire distributed to all undergraduate nursing students at both universities. The data collection will be repeated every year; at the start of the semester, each fall, for as long as the project is active, but at least for the minimum duration of the project that is 7 years. The questionnaire will be distributed and gathered by research members who have no educational relationship with the students. Information to the students will emphasize the process of anonymity and the students' right to withdraw from the study at any time. The questionnaire is distributed in a paper form to further the students' feeling of anonymity, and the students are informed that they can choose to submit the questionnaire blank or choose to not submit it at all.

The questionnaire poses questions about general information technology (IT) usage, eHealth, and attitudes to technology and about how experiences of eHealth are handled during education. In addition to this quantitative part, a number of qualitative studies will be conducted where different types of questions will be highlighted from an in-depth perspective. To make global comparisons, the data collection will be broadened to include parts from low- and middle-income countries as well as from high-income countries to get a global perspective. Contacts with other partner universities in Europe, Africa, and the United States have already been taken and may expand the study in the future.

The participants are recruited from BTH, Karlskrona, Sweden, and from the SRCUC, Stockholm/Huddinge, Sweden.

There is a distinct focus on IT and innovation for sustainable growth. At BTH, the main focus is to contribute to more sustainable societal development through higher education, research, and innovation. BTH conducts education and research at a high international level, focusing on IT integrated with other subjects such as engineering, industrial economics, spatial planning, design, and health care. In the field of nursing, education is offered at the undergraduate level, that is, the bachelor level and an advanced level, including more than 500 students enrolled in the Bachelor of Nursing Science Program (3 years).

The SRCU, founded in 1867, was the first secular nursing education institution in Sweden. The SRCUC is owned by the nonprofit foundation for the Red Cross University College, an affiliated foundation to the Swedish Red Cross. It is, mainly, a state-funded self-governed university. It offers higher education in nursing at the undergraduate level, the bachelor level, and an advanced level. At present, there are over 750 students enrolled in the Bachelor of Nursing Science Program (3 years). In Table 1 the demographics of the two participating universities are presented.

Table 1. Demographics of the study setting.

University college	Blekinge Tekniska Högskola	Swedish Red Cross University College, Autumn 2017
Nursing students (n)	560	721
Weeks in clinical practice (n)	33	33
eHealth[a] courses	Semester 3: eHealth[a] 4.5 ECTS[b]; Semester 5: eHealth, Selectable Course 7.5 ECTS. All additional lectures within the Bachelor of Science (BSc) program	Included in preclinical courses in semester 3 and the semester within the BSc program
"City size" or number of inhabitants	Karlskrona: 66,796	Stockholm: 1,515,017 and Huddinge: 110,003

[a]eHealth: electronic health.

[b]ECTS is the European Community Course Credit Transfer System where 1.5 Credits corresponds to 1 week of fulltime studies.

Inclusion Criteria

Undergraduate nursing students enrolled at the Bachelor of Nursing program at BTH and the SCRUC were eligible to participate in this study.

Data Collection

Sociodemographic Data

This includes age, sex, education, and work experience before nursing studies.

Internet Use (Frequency and Type of Use)

Questions are drawn from a selected subset in 2 major investigations: the EU investigation into individuals' use of ICT [58] and the World Internet Institute [59] common questions in collection of data on how people in different countries are using ICT and how this affects individuals, families, and society. This will allow for comparison with other populations. The possibility of creating scores from grouped variables will be evaluated and used in further analyses.

Outcome Measures

Electronic Health Literacy Scale

The ability to seek out, find, evaluate and appraise, integrate, and apply electronic resources toward solving a health problem is called eHealth literacy [60,61]. eHeals is an 8-question instrument for self-reported eHealth literacy skills [60] and will be used in this study to evaluate the nursing students' skills in using health technology. Stellefson et al [62] argue that the knowledge and skills necessary to conduct advanced eHealth searches are an important responsibility for the education community and that mere access to health resources does not ensure eHealth literacy. It can be a comparative advantage for nursing students to acquire the skills during their education for several benefits during their career. In a recent study [63], it was suggested that nurses with a high level of eHealth literacy had significantly positive overall health - promoting behaviors and skills to help patients and families find up-to-date, reliable, and quality health information. Moreover, 2 previous studies have investigated nursing students' eHealth literacy with the eHeals instrument in Jordan [64] and South Korea [65]. eHeals has been validated in other languages with a good result and will be translated into Swedish using backward-forward translation from the original English version. The construct validity of the Swedish version will be assessed in exploratory and confirmatory factor analyses, and internal consistency of the scale will be assessed using Cronbach alpha. A content validity index will also be created in the translation process.

Technophilia

For measuring the nursing students' personal feelings and attitudes toward technology in general, a measurement of technophilia will be used [66]. Technophilia is generally seen as a strong enthusiasm for modern technology. In the study by Seebauer et al [67], it is defined as "an attitude towards ICT, representing a sub-aspect of technology-related values, just as ICT is a subcategory of modern technology." Osiceanu [68] defines technophilia as an "attraction, enthusiasm of the human individual determined by the activities which involve the use of advanced technologies." Martínez-Córcoles et al [69] suggest that merely enthusiasm and desire are not enough to define technophilia but also an acquired need for (dependency), and joy of having the latest products and versions (technoreputation). According to Seebauer et al [67], openness toward technology and innovation influences personal dedication to certain technological artifacts and services, whereas feelings of low enthusiasm may work in the opposite direction.

Technology and Electronic Health in Nursing Education

This section comprises 2 components, each with 3 questions. The first component concerns how nursing students perceive the scope and content of eHealth in their current education. The second component deals with their perception of the importance and necessity of the knowledge of eHealth and their coming profession as nurses.

Statistical Analyses

Baseline characteristics will be tabulated using standard descriptive statistics, and bivariate correlations between variables will be analyzed with parametric and nonparametric measures. Additional data analysis (*t* test and analysis of variance [ANOVA]) will be used to investigate differences in eHealth and health literacy according to sociodemographic characteristics of the participants. The association between dependent variables and independent variables (health literacy, techPH, etc) will also be analyzed in various regression models before and after adjusting for background variables. To analyze changes over time, we will use instruments for longitudinal data analysis, for example, repeated measurements ANOVA.

In the validation process of the Swedish translation of eHeals, content validity, construct validity, and internal consistency will be assessed using exploratory and confirmatory factor analyses and internal consistency reliability analysis using Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp) and exploratory and confirmatory factor analyses with SPSS AMOS.

Qualitative Inquiry Substudy

The substudy has a qualitative design, and a subset of participating students at each university will be asked to participate in a substudy.

A separate study protocol and analysis plan will be developed before starting the qualitative substudy. The qualitative enquiry substudy will provide the perceptions and experiences from the individual participant's point of view to further develop knowledge based on the results and findings of the quantitative study.

An interview guide will be used consisting of a general question "Can you please tell me about your perception or experience of eHealth?" followed by more specific questions on private versus educational experiences of eHealth and probe questions such as "Tell me more…Can you explain further...Elaborate on that..."

Ethics

The questionnaire does not collect sensitive data that can be linked to any individual and is anonymous. The students can choose not to participate in the study. As students are a vulnerable population, the anonymous questionnaires were distributed and gathered by research members who had no educational relationship with the students. Information was emphasized on the process of anonymity and the students' right to withdraw from the study at any time.

Regarding the qualitative substudy, students will be invited by means of an information letter handed out by the research team. Those who accept to participate will receive verbal and written information about the study and information on their right to withdraw at any time. To ensure compliance with the Data Protection Act, data will be coded to protect and ensure the participants' anonymity and will be stored securely.

For the qualitative substudy, ethical approval will be obtained from the regional committees of ethics in Stockholm and south Sweden, depending on the issues that will be handled in this part of the study. Written informed consent will be obtained from the participants in the substudy. Confidentiality will be ensured for all participants in the project.

The results will be published in scientific journals but will also be made available in such a way that they can be used for feedback to the educational development work at the respective academic institutions.

The database used for the unidentified data is located physically at BTH and is used for several other clinical studies, including the Swedish National Study of Aging and Care, following all relevant protocols for data security and integrity.

Dissemination

Data will be presented on the group level only, ensuring that individual participants cannot be identified. The findings will be published in national and international peer-reviewed scientific journals and presented at relevant scientific conferences. The deidentified data will be posted in an open access data repository in accordance with the requirements of the scientific journal. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines.

Results

The study is ongoing. Data analysis is currently underway, and the first results are expected to be published in 2019.

Discussion

This study describes a project aimed at investigating nursing students' knowledge and attitudes to digitization and eHealth. The eNursEd study will answer several important questions about nursing students' attitudes toward and use of ICT in their private life, their education, and their emerging profession. Some questions in this study have been addressed previously and are in focus in other ongoing research projects. A special feature of this study is that several different factors are studied at the same time, with a large number of participants and the long time span over which they will be followed. This allows comparison and measurement of progress throughout the entire education. It will also give answers about how the use of internet and technology develops in separate groups over time.

Knowledge from this study will be used to compare different nursing education programs and students' knowledge about and relation to technology and eHealth. Results will also be communicated back to nursing education to improve the teaching of eHealth, health informatics, and technology in a nursing curriculum.

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Conflicts of Interest

None declared.

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Abbreviations

ANIA: American Nursing Informatics Association
BTH: Blekinge Tekniska Högskola
CNA: Canadian Nurses Association
CNIA: Canadian Nursing Informatics Association
eHealth: electronic health
EU: European Union
ICT: information and communication technology
IT: information technology
mHealth: mobile health
SRCUC: Swedish Red Cross University College
UHC: universal health coverage
WHO: World Health Organization

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Protocol

An Analytical Mobile App for Shared Decision Making About Prenatal Screening: Protocol for a Mixed Methods Study

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Abstract

Background: Decisions about prenatal screening to assess the risk of genetic conditions such as Down syndrome are complex and should be well informed. Moreover, the number of available tests is increasing. Shared decision making (SDM) about testing could be facilitated by decision aids powered by mobile technology.

Objective: In this mixed methods study, we aim to (1) assess women's needs and preferences regarding using an app for considering prenatal screening, (2) develop a decision model using the analytical hierarchy process, and (3) develop an analytical app and assess its usability and usefulness.

Methods: In phase 1, we will assess the needs of 90 pregnant women and their partners (if available). We will identify eligible participants in 3 clinical sites (a midwife-led birthing center, a family practice clinic, and an obstetrician-led hospital-based clinic) in Quebec City and Montreal, Canada. Using semistructured interviews, we will assess participants' attitudes toward mobile apps for decision making about health, their current use of apps for health purposes, and their expectations of an app for prenatal testing decisions. Self-administered questionnaires will collect sociodemographic information, intentions to use an app for prenatal testing, and perceived importance of decision criteria. Qualitative data will be transcribed verbatim and analyzed thematically. Quantitative data will be analyzed using descriptive statistics and the analytic hierarchy process (AHP) method. In phase 2, we will develop a decision model using the AHP whereby users can assign relative importance to criteria when deciding between options. We will validate the model with potential users and a multidisciplinary team of patients, family physicians, primary care researchers, decision sciences experts, engineers, and experts in SDM, genetics, and bioethics. In phase 3, we will develop a prototype of the app using the results of the first 2 phases, pilot test its usefulness and usability among a sample of 15 pregnant women and their partners (if available), and improve it through 3 iterations. Data will be collected with a self-administered questionnaire. Results will be analyzed using descriptive statistics.

Results: Recruitment for phase 1 will begin in 2019. We expect results to be available in 2021.

Conclusions: This study will result in a validated analytical app that will provide pregnant women and their partners with up-to-date information about prenatal screening options and their risks and benefits. It will help them clarify their values and enable them to weigh the options to make informed choices consistent with their preferences and values before meeting face-to-face with their health care professional. The app will be easy to update with the latest information and will provide women with a user-friendly experience using their smartphones or tablets. This study and the resulting app will contribute to high-quality SDM between pregnant women and their health care team.

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KEYWORDS

shared decision making; multiple criteria decision analysis; analytic hierarchy process; decision aid; prenatal screening; mobile app

Introduction

Prenatal Testing

Prenatal screening for trisomies 21 (Down syndrome), 18 (Edwards syndrome), and 13 (Patau syndrome) and for open neural tube defects has been offered to expecting women and couples for 3 decades. This type of screening differs from most disease screening programs in that it is not promoted as a public health means to reduce the incidence of the detected conditions. It is rather construed as a means to promote the reproductive autonomy of pregnant women and their partners, aiming to provide them with information that may be relevant to their reproductive decision making. Such decisions would be based on their knowledge about the fetus as well as their values and preferences [1]. Hence, prenatal screening is not meant to be a tool for promoting pregnancy termination for affected fetuses. Many pregnant women and couples choose to terminate pregnancies when the fetus is diagnosed with a trisomy [2], and some advocacy groups express concerns about screening contributing to stigmatization of disabled individuals [3]. Prenatal screening tests indicate a probability of the fetus having a given condition, but a diagnostic test is needed to confirm the result. Diagnostic tests such as amniocentesis and chorionic villi sampling do provide definitive results but entail a small risk of miscarriage. Thus, prenatal screening may reduce the number of invasive tests and their associated pregnancy losses. Testing also enables couples to prepare for the birth of a child with special needs, who is likely to benefit from specialized pregnancy follow-up and specialized care at birth and beyond [4].

However, the decision to undergo the initial probability screening leads to furthermore challenging decisions. Positive screening results lead to a further decision about the more invasive diagnostic testing. If this diagnostic result is positive, women face an even more difficult decision: whether to terminate the pregnancy or not. Some people prefer not to engage in this decision-making process in the first place. Reasons for declining screening include a preference for a less medicalized way of experiencing the pregnancy; an ideological, political, or religious opposition to screening; accepting the risks of having a child with the conditions tested for; preferring not to know in advance; and practical constraints [5-7]. Therefore, the option of choosing to decline screening must be available. Pregnant women and their partners must be adequately informed about the risks (or potential future risks) and benefits of screening tests and understand that such tests are optional and that they will be fully supported regardless of the path they choose [8].

Shared Decision Making and Multiple Criteria Decision Analysis

Many women and their partners are unaware of the implications of embarking on the path of prenatal testing [9]. The complexity of the testing decisions requires that the offer of testing be accompanied by (1) neutral, balanced, and comprehensive information on testing options and the conditions that are being detected, and (2) a space for making these very personal decisions in a way that is free of undue influence [9-11]. This reflects the fact that informed choice and free choice are basic components of an autonomous decision.

Women and their partners can be accompanied in this way through shared decision making (SDM), a process by which patients and clinicians collaborate to make decisions based on accurate information and on what matters most to them [12]. Decision aids (DAs) are SDM tools that can take various forms (such as a brochure, a booklet, an app, or a Web page). They provide information and solicit patients' values and preferences [13]. A Cochrane systematic review showed that DAs increase participants' knowledge, the accuracy of their risk perceptions, and the match between their values and the option chosen. In addition, it showed that DAs decrease decisional conflict (or discomfort) relating to feeling uninformed, decrease indecision about personal values, and decrease the proportion of people who are passive in the decision-making process [13]. Therefore, SDM and DAs work well with the reproductive autonomy rationale underlying prenatal screening, and SDM has been identified by patients as a preferred approach to guide decision making.

Once women and their partners have made a decision to undergo prenatal screening, they must choose from an increasing number of screening options and consider multiple and often conflicting decision criteria [14,15]. For example, the risk of false positives (false alarm) or false negatives (false reassurance) for each test, the longer or shorter wait times for the results and the variable costs and coverage schemes. In addition to best evidence about risks and benefits, decisions need to be informed by what

couples consider most important, that is, their preferences and values. For instance, a test involving new technology may be costly but may give the results in less time and with higher accuracy than one covered by insurance. Thus, couples need to decide whether finding out more accurate results and sooner is more important to them than the cost of the test, and if so, how much more important.

People usually have difficulty in making decisions when they face complex problems with multiple options involving value-based trade-offs between the advantages and disadvantageous of each option [16]. Multiple criteria decision analysis (MCDA) is an umbrella term for a number of methods for evaluating multiple conflicting criteria in decision making (both quantitative and qualitative criteria). These methods could help women decide among the multiple options for prenatal screening based on their values [17]; however, to the best of our knowledge they never been used in this context.

The analytic hierarchy process (AHP) is one MCDA method that has been used successfully (alone or integrated with other methods) in numerous medical decision-making contexts and in complex circumstances such as medication decision making in type 2 diabetes [18], priorities regarding colorectal cancer screening [19], prioritizing orthopedic patients for elective surgery (integrated with other methods) [20], and for prioritization of organ transplant patients [21]. The steps of the AHP match well with the essential elements of SDM. The SDM steps are as follows: define the problem and options available, review pros and cons of options, elicit patient values and preferences, clinician recommendations, review patient's ability to implement plan, check understanding, and make or defer the decision [22]. For example, for reviewing the pros and cons of the various tests, the corresponding AHP step is to make pairwise comparisons about how well the options satisfy the decision criteria; and for the SDM step of eliciting patient values and preferences, the AHP step is to make pairwise comparisons to prioritize value-based criteria affecting the decision [17]. The AHP is a quantitative technique but it can consider both quantifiable and nonquantifiable criteria. It is methodologically sound, systematic, and user friendly. It frames a decision as a hierarchy, which makes it easy to explain, and all inputs consist of consecutive comparisons of pairs of decision elements (eg, decision criteria and options). These *pairwise comparisons* are considered to be one of the best ways to elicit judgments from people [17] and seem well suited to app-based DAs.

Recent studies indicate an increase in the use of mobile phones and other wireless technology for health care purposes (mobile health [mHealth]) [23]. More than 85% of clinicians are now owners of smartphones and approximately 50% of them use smartphone apps in their clinical practice [24]. In the United States, a nationwide survey in 2012 reported that 33% of cellphone owners used mobile phones for health information, whereas 2 years earlier this was only 17% [25].

Even though mHealth tools cannot replace face-to-face communication with health care professionals during a consultation, as a form of DA they can be an important complementary and support tool. A well-designed app for health care purposes is accessible, has easy-to-follow procedures, and can automatically integrate the latest medical evidence. This could support SDM, improve clinical outcomes, and result in positive lifestyle changes [26,27].

Context

In the province of Quebec, Canada, pregnant women are followed up in hospital obstetrics departments, birthing centers, and family practice groups and are routinely offered 2 Down syndrome prenatal screening tests: (1) the serum integrated prenatal screening (SIPS), involving 2 blood tests (at 10-13 weeks, then at 14-16 weeks); (2) integrated prenatal screening (IPS), involving the same 2 tests, plus a nuchal translucency test based on a fetal ultrasound (11-14 weeks). Noninvasive prenatal testing (NIPT), or cell-free fetal DNA screening, which involves 1 blood test at 9 weeks and offers a higher level of reliability, is not yet covered by provincial health insurance in Quebec but can be purchased privately. For women whose SIPS or IPS results show a high risk of bearing a child with Down syndrome, public insurance will cover the NIPT test as of 2019. If these test results are positive, patients are offered amniocentesis.

Earlier, we developed a paper-based DA following a rigorous procedure [28] and subsequently updated it with the latest tests and an innovative decision model [29]. For the update, first we looked for recent evidence on prenatal screening and considered other prenatal screening DAs that included the new NIPT test. The development team reached consensus on which of the latest evidence should be considered. Data were updated, added, or removed from the DA in consequence, and a new selection hierarchy was incorporated to facilitate patients' selection of screening tests. The updated DA obtained a score of 16 out of 16 on the International Patient Decision Aids Standards checklist (Multimedia Appendix 1). Finally, the development team reached consensus on the final updated version of the DA. Usability, usefulness, and acceptability of this DA have been evaluated in another project with 45 couples in Quebec City, Canada.

The overarching aim of this study is to empower pregnant women and their partners with mobile technology so they can make informed decisions about prenatal screening with the support of their health care team. Thus, our specific objectives are to (1) assess the needs and preferences of pregnant women regarding the use of an app for deciding about prenatal screening, (2) develop a decision model using the AHP, and (3) develop an analytical app and assess its usability and usefulness.

Methods

Study Design

We propose a multipronged mixed methods study design in 3 phases: (1) needs assessment, (2) decision model development, and (3) analytical app development and pilot testing for usefulness and usability (Figure 1). As health care in Canada, including prenatal screening programs, is delivered under provincial and territorial rather than federal health insurance plans, we will focus on the province of Quebec. Quebec is a largely French-speaking province in Eastern Canada with over

8 million inhabitants. We will conduct our study in Quebec City and Montreal.

This project will be guided by a multidisciplinary steering committee of experts in SDM (FL, SAR, AG, and PA), family medicine and primary care (FL), prenatal care and genomics (FR, JCF, SL, and VR), engineering and technology (SAR), bioethics (VR), knowledge translation (FL, AG, PA, and SAR), and decision sciences and MCDA methods (SAR and JD). Patient representatives (pregnant women or women who have experienced pregnancies and their partners) will be involved in each phase to validate the decision model, determine the content of the app, and design it. The study has been approved by the ethics committee of the Population Health and Primary Care Research Division of the Centre intégré universitaire de santé et de services sociaux de la Capitale nationale (#2019-1534).

Phase 1: Needs Assessment

Participants

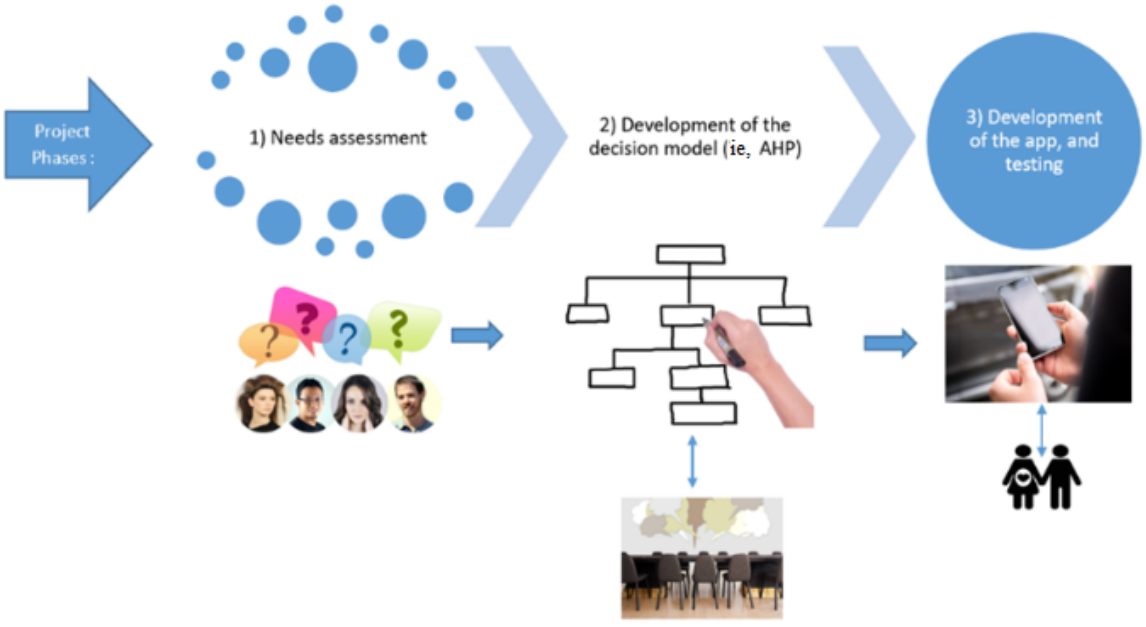
Using purposeful sampling, we will recruit a sample of 15 potential end users of the app (women and their partners if available), in each of the 3 clinical sites (midwife-led birthing centers, family practice clinics, and obstetrician-led hospital-based clinics) in Quebec City and Montreal for a total of 90 participants. An experienced research assistant and a trainee or 2 research assistants will meet pregnant women in the waiting rooms at each of these sites before their prenatal care appointment and invite those who are eligible to participate in the study. We expect to achieve theoretical saturation [30]. To be eligible to participate in both phases 1 and 3 of our study, pregnant women must (1) be at least 18 years old, (2) be more than 20 weeks pregnant or have given birth during the previous year (so as not to interfere with a decision about a current pregnancy), (3) have a low-risk pregnancy (ie, no complications such as hypertension or diabetes), (4) not be expected to give birth close to the data collection dates, (5) be able to speak and write either French or English, and (6) be able to give informed consent. Pregnant women's partners (if available and interested in participating in the study) will be asked to give informed consent. No eligibility criteria will be applied to the partners. If just 1 member of the couple but not both give informed consent, only the partner who gave consent will be interviewed. Pregnant women who are single are also eligible.

We chose these sites because all prenatal follow-up in the province of Quebec takes place in these 3 types of site. In addition, each attracts somewhat different clienteles, and we wanted to ensure that we include the needs and perspectives of as broad a spectrum of socioeconomic, ethnic, and linguistic communities (eg, immigrants and Anglophones) as possible in our study. We will recruit a minimum of 9 out of 45 participants from diverse ethnic and linguistic communities in Montreal and a minimum of 2 out of 45 in Quebec City to reflect the respective proportions of these population in the 2 cities [31].

Data Collection

Informed by recommendations about how to evaluate eHealth tools [32], and a study on needs assessments for mobile technology [33], we developed an interview guide to conduct semistructured interviews with couples or single participants to assess (1) their attitudes toward mHealth apps in general and for prenatal screening decisions in particular; (2) their current use (if any) of apps for the purpose of information seeking about health and decision making; (3) their opinions, suggestions, and preferences regarding an app for decision making about prenatal screening such as the one we are proposing.

Figure 1. Road map of the project. AHP: analytic hierarchy process.



Two trained research assistants or a research assistant and a trainee with expertise in health care research will conduct the interviews. No previous relationship will exist with participants other than a call or email contact to set a date for the interview.

According to participants' preferences, interviews will be conducted in a research center, in one of the recruitment sites, or in any other place convenient for them. Interviews will be conducted in French or English. Interviews are expected to last about 60 to 90 min. Written informed consent will be obtained at the beginning of the interview.

At the end of the interview, each participant or couple will be invited to fill out a self-administered questionnaire, validated by experts in the field, to (1) evaluate their intention to use an app for decision making about prenatal screening and (2) answer a series of questions (based on the AHP method) comparing the relative importance of various predefined decision criteria (see Figure 2) [29]. They will also complete a sociodemographic questionnaire.

Data Analysis

Interviews will be audio-recorded and transcribed verbatim. We will perform a thematic analysis while taking into account emerging themes. Two authors will separately code the transcripts using the NVivo qualitative data analysis software (QSR International Pty Ltd. Version 12, 2018). They will cross-check their codes and categorize the themes. They will then produce a report on the most relevant categories and an overview of the most important preferences, for example, features of the app that participants would like to see in a prototype (for phase 3).

Quantitative data will be analyzed using descriptive statistics. The AHP will be used to analyze the relative importance of decision criteria. We will adapt the CPD-Reaction (Continuing Professional Development Reaction) questionnaire, developed by our team to assess behavioral intention, to evaluate the intention of participants to use an app to decide about prenatal screening [34,35]. We will summarize sociodemographic characteristics and variables and compute scores from the adapted CPD-Reaction questionnaire; descriptive statistics such as mean, standard deviation, and median will be calculated for continuous data and frequencies for categorical data. The intention scores will be computed using the mean of the 2 intention items of the adapted CPD-Reaction. The reliability of the intention construct will be confirmed on these 2 items by Cronbach alpha testing with a level of statistical significance of less than .05. We will also perform bivariate analyses and multivariate analyses to assess participants' intentions to use an app for decision making. All variables will be entered in the multivariate model using the backward elimination procedure to obtain an adjusted model with better goodness of fit.

The example of questions related to the AHP are provided in Multimedia Appendix 2. The responses to these questions will be exported to a Microsoft Excel spreadsheet and will be analyzed using the AHP method explained below.

Phase 2: Development of the Decision Model Using the Analytic Hierarchy Process Method

In this phase, we will develop a decision model using the AHP method, based on the results of phase 1 and the content of our validated paper-based DA for prenatal screening [29] (Multimedia Appendix 1). The decision model will be guided by the routine prenatal screening procedure in the province of Quebec, Canada [36,37]. The 6 AHP steps suggested by Dolan et al for performing the AHP method to promote SDM [17] and Saaty's AHP [38] will be followed during the development of the decision model and its implementation in our app prototype. The 6 steps are described in the following sections.

Step 1: Define the Decision Elements and the Working Knowledge Base

This step consists of the following:

1. Defining the elements of the decision. The elements are the goal and decision, the options to be considered, and the criteria that will be used to determine how well the options meet the goal.
2. Examining the working knowledge base to see if there is a dominant option that is clearly better than the others across all of the decision criteria.

This first step was already accomplished during the development of the paper-based DA [29] (Multimedia Appendix 1).

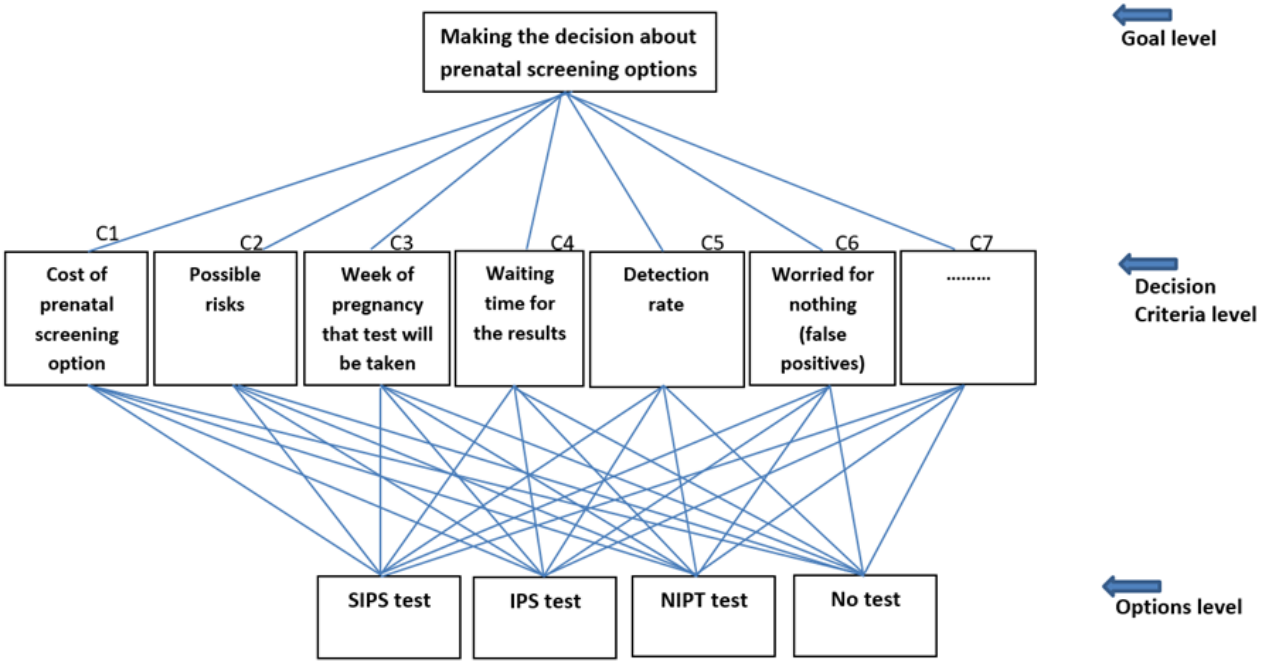
Step 2: Construct the Decision Model

The second step is to arrange the decision elements into a hierarchy. The prototype of the model for prenatal screening is shown in Figure 2. The goal is at the top, making a decision about prenatal screening; the options are at the bottom (SIPS, IPS, NIPT, and no test); and the decision criteria are in between.

Step 3: Divide the Decision into Smaller Parts and Make Pairwise Comparisons to Determine Local Priorities

In the AHP approach, the decision is analyzed by dividing it into smaller parts and creating comparison pairs between decision elements on lower levels of the hierarchy relative to each element on the next higher level [16]. In other words, decision options are compared relative to each criterion. Every possible pair will be compared. Comparisons can be verbal, numerical, or graphic. In this study, we will use the numerical comparison format, Saaty's 9-point scale [38]. Users will first be asked if the 2 elements being compared are equally important or preferable relative to the referent element on the next higher level of the hierarchy or if one is more important or preferable than the other. If they are equal, no further input is needed. If one is more important or preferable, the decision maker indicates how much more important or preferable on a scale of 1 to 9. For example, they will indicate if cost is more important to them than time or vice versa. After all the comparisons are completed, a comparison matrix will be created and then, using matrix algebra procedures, ratio scales will be created. These scales indicate the relative priorities of the criteria in meeting the goal and the priorities of each option considering each criterion [16,38].

Figure 2. Preliminary decision model. IPS: integrated prenatal screening, NIPT: noninvasive prenatal testing, SIPS: serum integrated prenatal screening.



Step 4: Synthesis

In this step, all of the scales created in step 3 will be combined to determine how well the options (ie, SIPS, IPS, NIPT, and no test) will meet the goal: an informed decision about prenatal screening that reflects patients' preferences. This can be done through either distributive synthesis, which ranks the options in order of preference, or ideal synthesis, which identifies a single best option. We will choose the most appropriate synthesis based on users' needs.

Step 5: Sensitivity Analysis

This is an optional but useful step. Sensitivity analyses will help determine how sensitive the selected option will be by changing one input while keeping the other inputs constant. It could help determine how the different judgments of the patients affect the analysis. The possibility of adding this step will be evaluated with expert team members and patient partners.

The final step is to either make the prenatal screening decision or go back and refine the analysis until a decision can be made. We will integrate the 4-item SURE (Sure of myself; Understand information; Risk-benefit ratio; Encouragement) screening test designed to screen for clinically significant decisional conflict [39] into our analytical app. If the pregnant women and their partners are not sure of their decision, they can go back and reconsider their options.

The steps of the model will be added to the app. Pregnant women and their partners will use this app to weight decision options based on their preferences and on what is most important to them, compare the available prenatal screening options in the light of these preferences, and finally select one. The decision model will be validated, after development, with a team of experts and patient partners in a meeting.

Phase 3: Development of the Analytical App and Pilot Testing

Development of the App

In this phase, we will employ a user-centered iterative approach to developing the mobile app. The app will be for mobile devices or tablets using leading operating systems such as Android and iOS. It will be written in the official development language of these operating systems. Users will not need access to the internet after downloading the app, except when updates become available. The app prototype will be developed in cooperation with a partner commercial company and in regular consultation with the patient partners.

The app will be divided into 4 main parts: (1) the information needed to make the decision, including the information on trisomy 21 (T21), trisomy 18 (T18), and trisomy 13 (T13), and the 4 different prenatal screening options (ie, SIPS, IPS, NIPT, and no screening), (2) the information on advantages and disadvantages of *doing the test* and *not doing the test*, (3) the AHP pairwise comparisons to weigh the criteria leading to a decision (advantages and disadvantages of each test and preferences), and (4) the SURE screening test to make sure the user is sure about their decision [39]. We will ensure the features of the app respond to the needs expressed in phase 1. This will be accomplished at meetings attended by the multidisciplinary expert team and the technology company.

Pilot Testing

After development of the first prototype, we will conduct pilot testing to evaluate the perceived usability and usefulness of the app and improve it iteratively. We will recruit a sample of 15 pregnant women and their partners (if available) consulting for prenatal care in the same 6 sites as in phase 1. Participants will be couples or individuals who participated in phase 1 and new participants will be recruited if needed to reach the targeted

sample size. Participants will be invited by personal email or phone or in person at the clinical sites. The same eligibility criteria as in phase 1 will apply.

Participants will be invited to use the app and give feedback. As this phase will be iterative, we will start by recruiting 5 couples. During semistructured interviews, lasting 60 to 90 min, we will ask them to assess the usability and usefulness of the prototype app based on a self-administered questionnaire, and then we will ask them for their suggestions for its improvement. Usability will be assessed using the system usability scale (SUS) [40]. SUS is frequently used to measure user experience and utility of information systems, including the efficacy and satisfaction with which users accomplish specific tasks. This scale comprises 10 statements that assess participants' immediate reaction to the use of a technology before any discussion with the researcher. The scale is also used to explore users' needs regarding a prototype or to evaluate the usability of an existing technology. Users will assess usefulness on a scale of 1 to 5. In addition, we will use the 10 items of the Preparation for Decision Making scale [41] to assess how useful the app is for preparing a respondent to communicate with their health professional at a consultation focused on making a prenatal testing decision. Participants' feedback in this first wave will be used to improve the app prototype, and then we will move into recruiting the next waves of 5 couples or individuals, repeating the same data collection process. In keeping with the literature and our previous work [42], we expect to reach saturation with a maximum of 3 waves of feedback [30].

Results

For phase 1 of this project (needs assessment), recruitment will begin in 2019. Recruitment and data collection will continue until 90 participants (45 in Quebec City and 45 in Montreal) have been interviewed. The results of phase 2 will lead to the development of the analytical decision model. The results of phases 1 and 2 will be integrated into phase 3 to develop the app. Following this step, the app will be pilot tested. All 3 phases of the study are expected to be completed in 2021. The reporting of results will follow the mHealth evidence reporting and assessment checklist [43], and the reporting of qualitative results will also follow the COnsolidated criteria for REporting Qualitative research guideline [44].

Discussion

Overview

By the end of the study, we will have developed and validated an analytical app that will provide pregnant women and their partners with the most up-to-date information about the various prenatal screening options and their risks and benefits, including the option of no testing. We expect this app to inform pregnant women and their partners and help them to consider various decision criteria in the light of the most recent information and their values to make a decision that they are comfortable with and hence provide truly informed consent to screening. It will enable them to rate the importance of criteria to be considered and finally share a decision consistent with their preferences and values with their health care professional. As with other forms of DA, health care providers can either accompany women and their partners through the process of using the mobile app or they can discuss the decision afterwards when the decision process is still fresh in the minds of their patients. The app will be user-friendly and easy to update with the latest information.

Finally, the proposed AHP method has a solid methodological base and is easy to use and integrate into SDM tools such as DAs to contribute to SDM. AHP can facilitate eliciting patient values and preferences, and we believe it is ideally suited to help pregnant women and their partners with various levels of health literacy to process this complex decision.

Strengths and Limitations

Our team has 15 years of experience in the development of shared decision-making tools and has been working on tools specifically for prenatal testing decisions for more than 5 years. To the best of our knowledge, the AHP approach has never been used in this context. Developing the AHP model will provide a systematic approach for helping pregnant women and their partners choose whether to undergo prenatal testing or not, and if so, what options match their preferences and values. Using pairwise comparisons, the AHP enables patients to consider both quantifiable (objective considerations such as cost and time) and nonquantifiable criteria (subjective considerations such as women's feelings and values) in the analysis. This method could be applied to other complex decisions.

In terms of limitations, recruiting 90 pregnant women with or without their partners in 3 different sites in 2 cities (Quebec City and Montreal) may be challenging. Second, the study targets couples in the province of Quebec, that is, in a single health care system, so we cannot infer that our results are applicable to other populations. Finally, enabling women and their partners to fully share their decision-making process with their health care provider after using the app may require further study.

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Authors' Contributions

SAR and FL are the grant holders and principal investigators for the project. SAR, FL, JCF, FR, VR, PA, and ACG conceptualized the study design. SAR had a major contribution in drafting the manuscript. All authors contributed ideas, read, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Decision Aid.
[PDF File (Adobe PDF File), 1702 KB - resprot_v8i10e13321_app1.pdf]

Multimedia Appendix 2
Questionnaire.
[PDF File (Adobe PDF File), 228 KB - resprot_v8i10e13321_app2.pdf]

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Abbreviations

AHP: analytic hierarchy process
CPD: continuing professional development
DA: decision aid
IPS: integrated prenatal screening
MCDA: multiple criteria decision analysis
mHealth: mobile health
NIPT: noninvasive prenatal testing
SDM: shared decision making
SIPS: serum integrated prenatal screening
SURE: Sure of myself; Understand information; Risk-benefit ratio; Encouragement
SUS: system usability scale

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Protocol

A Digital Intervention for Australian Adolescents Above a Healthy Weight (Health Online for Teens): Protocol for an Implementation and User Experience Study

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Abstract

Background: More than one-fourth of Australian adolescents are overweight or obese, with obesity in adolescents strongly persisting into adulthood. Recent evidence suggests that the mid-teen years present a final window of opportunity to prevent irreversible damage to the cardiovascular system. As lifestyle behaviors may change with increased autonomy during adolescence, this life stage is an ideal time to intervene and promote healthy eating and physical activity behaviors, well-being, and self-esteem. As teenagers are prolific users and innate adopters of new technologies, app-based programs may be suitable for the promotion of healthy lifestyle behaviors and goal setting training.

Objective: This study aims to explore the reach, engagement, user experience, and satisfaction of the new app-based and Web-based Health Online for Teens (HOT) program in a sample of Australian adolescents above a healthy weight (ie, overweight or obese) and their parents.

Methods: HOT is a 14-week program for adolescents and their parents. The program is delivered online through the Moodle app–based and website-based learning environment and aims to promote adolescents' lifestyle behavior change in line with Australian Dietary Guidelines and Australia's Physical Activity and Sedentary Behaviour Guidelines for Young People (aged 13-17 years). HOT aims to build parental and peer support during the program to support adolescents with healthy lifestyle behavior change.

Results: Data collection for this study is ongoing. To date, 35 adolescents and their parents have participated in one of 3 groups.

Conclusions: HOT is a new online-only program for Australian adolescents and their parents that aims to reduce cardiovascular disease risk factors. This protocol paper describes the HOT program in detail, along with the methods to measure reach, outcomes, engagement, user experiences, and program satisfaction.

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KEYWORDS

adolescent; overweight; diet; exercise behavior

Introduction

The Issue: Adolescent Obesity

At present, more than one-fourth of Australian adolescents aged 14 to 17 years are overweight or obese, which is significantly higher than 20 years ago [1]. High body mass index (BMI) in adolescence is difficult to reverse and persists into adulthood [2-5]. Previous findings from the American Bogalusa Heart Study, a longitudinal study with a mean follow-up of 17.6 years, showed the prevalence of obesity in adulthood was 86% for men and 90% for women among adolescents who had been obese between the ages of 15 and 17 years [4]. Adolescent obesity is associated with considerable short-term and long-term health consequences, such as increased risk of heart disease and diabetes [6,7]. These risk factors have also been shown to track into adulthood [2], which, in addition to the risk of being an obese adult, indicate a double burden of adolescent obesity on cardiovascular disease risk.

Why Target Adolescence?

Adolescence is a period of transition during which autonomy and independence increase. During this life stage, autonomy over food choice [8] and influence from peers can contribute to overweight risk behaviors, including unhealthy diets, insufficient physical activity, and excessive sedentary time [9,10]. Parent behaviors, healthy home food environments [11], peer support from friends [12], and social norms [13] can each influence adolescent lifestyle behaviors and are important to consider in developing interventions for this population. Typical changes to diet during adolescence include a decrease in breakfast consumption and increased frequency of snacking, fast food consumption, and eating outside of the home environment [14-16]. As a result, diet quality declines from childhood to adolescence [17]. Activity changes include a decrease in physical activity (especially in girls) and an increase in sedentary time [14,18,19]. As lifestyle behaviors are pliable and behaviors formed during adolescence have been shown to track into adulthood [3,14], it is important to intervene during this time to promote healthier behaviors. It has been recently suggested that mid-teen years represent a tipping point as the window of opportunity to prevent irreversible damage to the cardiovascular system caused by unhealthy lifestyle factors and excess BMI may close after this time [20].

Adolescents and Technology-Based Programs: The Evidence Gap

Adolescents are early adopters of technology and generally are innately accepting of innovative methods of communication and learning. In 2015, it was estimated that 65% of Australian teenagers aged 14 to 17 years used a mobile phone to access the internet, 74% used a computer to access the internet, and 80% had a smartphone [21]. Moreover, Australian adolescents aged between 15 and 17 years are the highest proportion of internet users (98%) [22]. Online programs have the capacity to achieve greater reach than face-to-face programs, as participants can be included irrespective of geography or means of transport to a physical location [23]. Although online-only programs exist for adult weight management [23], there is a paucity of online-only programs for secondary prevention of obesity in adolescents [24].

The Health Online for Teens Program

A new program, Health Online for Teens (HOT), is the first Australian online-only, expert-supported group intervention involving parental and peer support for obesity prevention in adolescents. HOT is underpinned by theories of behavior change and self-determination and recognizes the importance of engagement in lifestyle choices at a critical, yet pliable, period of transition. Covering the key areas of overcoming peer pressure, maintaining a healthy diet, and being physically active as well as emotional well-being, HOT provides opportunities for teens (and their parents) to gain improved lifestyles through goal setting and peer and expert support.

Study Aims

The objective of this study is to determine the feasibility of a new online healthy lifestyle program (HOT) to improve lifestyle-related behaviors in a sample of Australian adolescents above a healthy weight. Specifically, this study aims to (1) obtain feedback from a sample of overweight or obese teens who will be asked to discuss the content, features, and design of HOT and (2) determine the feasibility of HOT through pilot testing in a sample of up to 45 adolescents and collecting data on recruitment, retention, and engagement over the course of the 14-week program. This publication describes the study methods and rationale to achieve these research aims.

Methods

Design and Research Objectives

This study is a nonrandomized intervention feasibility trial [25] that aims to assess the acceptability, demand, implementation, and practicality of the HOT program. Accordingly, there is no control or comparator group in this study. The research protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000465257) on March 29, 2018. Ethics approval for this study was granted by the Flinders University Social and Behavioural Research Ethics Committee on March 21, 2018 (Project number 7896; Health Online for Teens: An Australian technology-based lifestyle program for overweight adolescents).

This paper reports the protocol of intervention and evaluation of HOT in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Multimedia Appendix 1) [26,27]. The findings of the study will be reported according to the Transparent Reporting of Evaluations with Nonrandomized Designs Statement [28]. Textbox 1 outlines the research objectives of this feasibility study.

Textbox 1. Research objectives in the Health Online for Teens (HOT) feasibility study.

- To assess engagement and use of the HOT program and its components and Health Online for Teens chat-bot (HOT-BOT) by teenage participants
- To assess engagement and use of HOT and parent resources by parents or caregivers of the participants
- To determine the reach of HOT recruitment and representativeness of the target population
- To determine the effectiveness of the program to support teenagers to achieve healthy lifestyle goals and improve weight, diet and activity behaviors, and self-perception (outcome evaluation)
- To determine program satisfaction and process evaluation data from participants
- To conduct focus groups and/or interviews to deeply explore the participants' HOT experience, thoughts on the content, appearance and design of the program and its elements, and barriers or enablers to engagement

Population

Australian adolescents will be recruited from the community through social media advertising. Adolescent participants express interest to participate in the study through an online survey administered through Qualtrics (Qualtrics). Qualtrics is an online survey tool that is supported by the researchers' host institution. Adolescents expressing an interest to participate will be screened against several inclusion and exclusion criteria. Eligible adolescents include girls and boys, aged between 13 and 17 years at enrollment, who are above a healthy weight for their age and gender, not pregnant or breastfeeding, with access to Wi-Fi at home. Eligible parents or caregivers of included adolescents can be of any age, and typically, 1 to 2 parents or caregivers are anticipated to be included for each adolescent. Adolescent participants will be identified as above a healthy weight (overweight, obese, and morbidly obese) using self-reported height and weight and weight status from BMI (International Obesity Task Force [IOTF] extended criteria) [29]. Groups are planned to commence when there are a minimum of 10 eligible adolescent and parent dyads who provide their consent to participate. Parents will provide informed consent for themselves and their child to participate, and children will provide informed assent to participate in the form of scanned hardcopy consent forms, electronically signed sheets, or upon commencement of baseline surveys administered online. Copies of participant information sheets and consent and assent forms are provided in Multimedia Appendix 2 as per the SPIRIT Checklist [26,27].

Intervention

The online HOT program aims to support overweight or obese adolescents to improve their lifestyle, through setting goals and making sustainable changes to diet and activity patterns. The HOT program aims to improve knowledge on healthy diet, activity, and emotional well-being and build skills and capacity for teens to plan ahead, set their own goals, and reflect and evaluate on their progress. The HOT program encourages participants to seek support from parents and peers to facilitate a home improvement, which is supportive of a healthy lifestyle and self-esteem.

The HOT program has a number of principles that inform program targets and strategies that are promoted to achieve the targets (Table 1). These targets are underpinned by national guidelines [30-32] and other evidence-based recommendations [33-36]. The HOT program also aims to build capacity and resilience in teenagers to identify barriers toward a healthy lifestyle, plan ahead, and take small steps and sustainable changes to overcome these. The HOT program incorporates a number of behavior change techniques [37] including providing information on consequences of behavior in general, providing normative information about others' behavior, goal setting (behavior); barrier identification or problem solving, prompting self-monitoring of behavior, prompting a focus on past success, providing information on where and when to perform the behavior, providing instruction on how to perform the behavior, using of follow-up prompts, planning social support or social change, and relapse prevention or coping planning.

Goal setting is a key element of HOT, and although HOT participants set their own goals around diet and activity and monitor their progress, HOT aims to address common adverse behaviors for adolescents, including skipping breakfast, frequent fast food intake, high levels of sedentary behavior, and low levels of physical activity, by encouraging individual goal setting in these areas. HOT employs the use of SMART goals [39] that are specific, measurable, achievable, realistic, and time bound. An outline of each week of the program, including the context for individuals to conceptualize their own SMART goals, is presented in Table 2. In addition to HOT sessions that are accessed through Moodle, a supportive and motivational chatbot (HOT-BOT) is built into the HOT program to collect information on teen goals and prompt them to complete the program tasks for the week, set their goals, and reflect on their progress. HOT-BOT is delivered through Facebook Messenger and operates on the Chatfuel platform [40]. Facebook Messenger was selected for the HOT-BOT, as Facebook is widely used and accepted by both adolescents and their parents. The Facebook Messenger platform is also compatible with the chatbot technology, whereas other social media platforms commonly used by adolescents do not support this technology (eg, SnapChat and Instagram).

Table 1. Health Online for Teens (HOT) lifestyle behavior principles, targets, and strategies for adolescents.

Domain	HOT principles	HOT targets	HOT strategies	References
Diet	Eat a wide range of core foods every day based on the Australian Guide to Healthy Eating (AGHE)	Aim to eat the following: 2 serves of fruits per day; 5 serves of vegetables per day; Wholegrain and wholemeal cereal-based products (bread, pasta, rice, and cereals); Low-fat dairy and lean meat products	Plan healthy meals and snacks ahead of time; Take a packed lunch to school; Include fruits and/or vegetables in every meal; Get involved in food planning, shopping, preparation, and cooking; Try healthy recipes; Encourage family meals	Australian Dietary Guidelines (ADG) [31] and the AGHE [32]; Larson *et al*, 2007 [38]
Diet	Limit discretionary foods and choose healthy snacks instead	Aim to limit the number of discretionary foods each week	Choose fruits and vegetables as snacks and swap discretionary foods (chips, chocolates, muesli, and snack bars) for healthy snacks; Plan snacks ahead of time and pack healthy snacks for school and other daily activities	ADG [31] and the AGHE [32]
Diet	Replace sweetened soft drinks, sports drinks, energy drinks, flavored milk, and cordial with water	Aim to drink 2 L of water per day and avoid sweetened beverages (cordial and soft drinks)	Pack a water bottle with you wherever you go; Refill at water fountains at school and when on the go; On hot days, freeze water overnight for a refreshing drink during the day	ADG [31] and the AGHE [32]; Healthy Kids (NSW Health) [33]
Physical activity	Be active every day	Aim to do at least 1 hour of moderate to vigorous intensity physical activity every day	Incorporate physical activity in everyday life; it is fun and a great way to spend time with people.	Australia's Physical Activity and Sedentary Behaviour Guidelines [30]
Physical activity	Be active every day	Aim to include strengthening exercises in physical activity at least 3 times per week	Include activities that build strength for strong muscles and bones; these do not need to be gym-based.	Australia's Physical Activity and Sedentary Behaviour Guidelines [30]
Sedentary behavior	Minimize time spent looking at screens (eg, TV, phone, computer, and iPad)	Aim for no more than 2 hours in screen-based activities (outside school hours and not including homework)	Plan specific periods of time for watching TV and using other screen devices; Plan for active and outdoor activities with friends over watching TV and playing computer games; Choose active travel options where possible	Australia's Physical Activity and Sedentary Behaviour Guidelines [30]
Sedentary behavior	Minimize sedentary time	Limit prolonged periods of sitting (>30 min)	Try to get up and move regularly when at home and when possible at school	Australia's Physical Activity and Sedentary Behaviour Guidelines [30]
Sleep	Get plenty of sleep each night	Aim for 8-10 hours of quality sleep per night	Avoid using screens in the bedroom and avoid screen use just before bedtime; Establish a relaxing bedtime routine	National Sleep Foundation (US) [34]; Australian Centre for Education in Sleep [36]; Better Health Channel (Vic Health) [35]
Well-being	Develop and maintain positive relationships with self, family, friends, and peers	Treat others with respect in the way you would like to be treated; Listen to and respect others' points of view; Suggest solutions to problems and be encouraging; Avoid toxic relationships—online and in real life; Increase self-awareness and learn principles of mindfulness	Treat others with respect in the way you would like to be treated; Listen to and respect others' points of view; Suggest solutions to problems and be encouraging; Avoid toxic relationships—online and in real life; Increase self-awareness and learn principles of mindfulness	—[a]
Well-being	Be a positive influence and encourage healthy behaviors in others	Encourage and support healthy behaviors; Be a role model for others; Share enthusiasm and positivity for healthy lifestyles	Encourage and support healthy behaviors; Be a role model for others; Share enthusiasm and positivity for healthy lifestyles	—

[a]Not applicable.

Table 2. Health Online for Teens (HOT) program outline.

Time			Weekly session content	Weekly activities
Week	Days in	Days to go		
Preprogram	−7 to 0	99 to 105	N/A[a] evaluation and reflection	Preprogram evaluation
1	1 to 7	93 to 98	Introduction and welcome—live session: What is HOT?	Rules of communicating in HOT—dos and don'ts of participating in forums and chats; Introduction to your HOT group (forum)
1	1 to 7	93 to 98	How to find your way around HOT;	To do: introduction to your HOT group (forum)
1	1 to 7	93 to 98	Introduction to HOT Targets (Table 1)	Health Online for Teens chatbot (HOT-BOT) setup
2	8 to 14	85 to 91	Nutrition: how your diet impacts health; Introduction to the Australian Guide to Healthy Eating and the Australian Dietary Guidelines	To do: Healthy Eating Quiz [41] and forum discussion of results
2	8 to 14	85 to 91	Activity: what is physical activity and sedentary behavior?	To do: keep a physical activity and screen time diary
2	8 to 14	85 to 91	Well-being: benefits of peer and parental support	HOT-BOT check in
2	8 to 14	85 to 91	Making changes: setting SMART (Specific, Measurable, Achievable, Realistic, and Timely) goals and changing behaviors	
3	15 to 21	78 to 84	Nutrition: the 5 core food groups and the other discretionary foods and complete the food group quiz	To do: keep a diary of what foods you normally eat on a weekend day and weekday
3	15 to 21	78 to 84	Activity: what are the physical activities and sedentary behavior guidelines	To do: reflect on how much activity you do each day; compare weekday with weekend day
3	15 to 21	78 to 84	Well-being: finding and giving support and supportive environments	To do: identify barriers to healthy eating and possible solutions
3	15 to 21	78 to 84	Making changes: what are barriers and what are enablers?	My goals: set a SMART goal to be more physically active
3	15 to 21	78 to 84		HOT-BOT check in
4	22 to 28	71 to 77	Nutrition: healthy dietary fats	To do: reflect on your diet on weekend/nonweekend days: how does it compare?
4	22 to 28	71 to 77	Activity: benefits of physical activity	My goals: set a SMART goal to try a new physical activity with a friend or family member
4	22 to 28	71 to 77	Well-being: what is body image	HOT-BOT check in
4	22 to 28	71 to 77	Making changes: reviewing your goals: are they SMART?	
5	29 to 35	64 to 70	Nutrition: importance of breakfast; healthy breakfast ideas	To do: body functionality writing task (modified from [42])
5	29 to 35	64 to 70	Activity: barriers to physical activity (busy lives, neighborhoods, and safety) and tips for exercising safely in the neighborhood	My goals: set a SMART goal to: eat a healthy breakfast and try a physically active alternative to watching TV or playing videogames with a friend
5	29 to 35	64 to 70	Well-being: positive body image	HOT-BOT check in
5	29 to 35	64 to 70	Making changes: being realistic	
6	36 to 42	57 to 63	Nutrition: healthy lunches and snacks for school	My goals: set a SMART goal to: improve lunches and snacks for school this week and try a new strengthening exercise
6	36 to 42	57 to 63	Activity: strength building activities and what makes us strong	HOT-BOT check in
6	36 to 42	57 to 63	Well-being: physical activity and health and mental well-being	
6	36 to 42	57 to 63	Making changes: goal setting review	

Time			Weekly session content	Weekly activities
Week	Days in	Days to go		
7	43 to 49	50 to 56	Nutrition: proportion of food groups in balanced dinner meals and healthy recipe videos	My goals: set a SMART goal to: cook dinner for your family one night this week and reduce screen time this week
7	43 to 49	50 to 56	Activity: strategies to reduce (nonhomework) screen time	HOT-BOT check in
7	43 to 49	50 to 56	Well-being: building resilience	
7	43 to 49	50 to 56	Making changes: building on your goals	
8	50 to 56	43 to 49	Nutrition: choosing healthier takeaway foods	To do: watch the Dove real beauty campaign and think about how the media can control what we see
8	50 to 56	43 to 49	Activity: do you spend too much time attached to devices (eg, checking social media and texting)?	To do: find and appraise a source of nutrition or physical activity advice on social media
8	50 to 56	43 to 49	Well-being: how can media/social media makes us feel and why?	My goals: set a SMART goal to: choose a healthier takeaway meal and use social media less this week
8	50 to 56	43 to 49	Making changes: review at the halfway point	HOT-BOT check in
9	57 to 63	36 to 42	Nutrition: choose water over sugary drinks	To do: sugar drinks quiz
9	57 to 63	36 to 42	Activity: choose active transport over inactive options	To do: keep a sleep diary this week
9	57 to 63	36 to 42	Well-being: being cyberaware and being safe online	My goals: set a SMART goal to: drink more water/less soft drink and take an active transport option
9	57 to 63	36 to 42	Making changes: how to stay motivated	HOT-BOT check in
10	64 to 70	29 to 35	Nutrition: label reading and selecting items	To do: read labels of some common foods/snacks/drinks at home
10	64 to 70	29 to 35	Activity: what are the sleep recommendations	My goals: set a SMART goal to improve your sleep
10	64 to 70	29 to 35	Well-being: overcoming peer pressure	HOT-BOT check in
10	64 to 70	29 to 35	Making changes: how to cope with relapse	
11	71 to 77	22 to 28	Nutrition: healthy and easy food swaps at home and away and recipe modification	To do: complete the sleeping habits checklist quiz
11	71 to 77	22 to 28	Activity: sleeping habits and sleep hygiene	My goals: set a SMART goal to choose a recipe and make it healthier
11	71 to 77	22 to 28	Well-being: increasing your self-awareness	HOT-BOT check in
11	71 to 77	22 to 28	Making changes: how to prevent relapse, healthy eating at parties and celebrations	
12	78 to 84	15 to 21	Nutrition: why we eat—hunger and satiety, mindful eating	To do: reflect on why you eat (mindless eating reflection task)
12	78 to 84	15 to 21	Well-being: self-awareness and mindfulness	To do: eat a meal mindfully and intuitively
12	78 to 84	15 to 21	Making changes: sustainability and long-term changes	My goals: set a SMART goal to make changes to your sleep routine
12	78 to 84	15 to 21		HOT-BOT check in
13	85 to 91	8 to 14	Nutrition/activity/well-being: Review of HOT targets; Lifestyle behaviors can be related to each other; Bringing all these behaviors together to have and maintain a healthy lifestyle	To do: mindful physical activity exercise
13	85 to 91	8 to 14	Making changes: maintaining healthy lifestyle changes and relationships	My goals: set SMART lifestyle (diet and activity) goals you want to maintain after HOT
13	85 to 91	8 to 14		To do: think about how you can maintain goals and HOT target behaviors (identify barriers and enablers)
13	85 to 91	8 to 14		HOT-BOT check in

Time			Weekly session content	Weekly activities
Week	Days in	Days to go		
14	93 to 98	1 to 7	Program review—what have we all achieved?—live session	To do: Healthy Eating Quiz and reflection on diet changes during HOT
14	93 to 98	1 to 7	How far have we come and where to from here	To do: review of goals for after HOT
14	93 to 98	1 to 7	Where to get help/support after HOT	HOT-BOT goodbye
Postprogram	99 to 105	−7 to 0	N/A evaluation and reflection	Postprogram evaluation

[a]N/A: not available.

Program Access

Adolescents participating in HOT will be loaned an iPad Mini for the duration of the project. The iPad is configured with the apps required for the project (Moodle and Facebook Messenger) and will be delivered to the adolescents approximately 1.5 weeks before they start the program. On safe return of equipment at the end of the program, families will receive an Aus $50 gift card for either Apple iTunes/App Store or Coles Myer in recognition of their contribution to this study. Adolescents will be provided with their HOT login and will be able to log in to Moodle from any other device as they wish. Parents will not be loaned any device during HOT but will be given a login to access HOT for themselves using their own personal devices (smartphone or tablet) or computer (desktop or laptop). Parents and adolescents will have access to the same HOT content; however, there will be separate spaces for parents and adolescents to connect with their peers through a discussion forum. In addition to HOT sessions, parents will have access to specifically tailored information including supporting your teen to meet HOT targets, communicating with your teen, your teen and body image, healthy lifestyle guidelines for adults (diet, activity, and sleep), and a collection of additional parent resources (Web links).

Evaluation

A mixed-methods approach comprising quantitative and qualitative evaluation will be used to evaluate the feasibility of HOT. This project aims to evaluate the feasibility of HOT, including population characteristics (program reach), program outcomes (indication of program effectiveness), processes (program implementation), engagement (program use), and acceptability (program satisfaction) measures. A summary of measures and the time of assessment are described in Multimedia Appendix 3. Specific primary outcomes and secondary outcomes of interest are listed in Table 3.

Table 3. Primary and secondary outcomes and their assessment.

Outcomes	Assessment method	Time point
Primary outcomes		
User engagement (adolescents and parents) with the program	Access of 14 program sessions, expressed as a proportion of content covered as measured by Moodle metrics	From the start to the end of the program (14 weeks)
Adolescent self-reported weight status	Height and weight used to calculate BMIz[a] [43] and International Obesity Task Force extended weight status [29]	Change from preprogram (enrollment) to postprogram (after 14-week intervention)
Secondary outcomes		
Adolescent diet behavior	Children's Dietary Questionnaire [44] and Serves of Core Foods [45]	Change from preprogram (enrolment) to postprogram (after 14-week intervention)
Adolescent physical activity behavior	7-day 24-hour accelerometry, GENEActiv Original wrist-worn accelerometer [46] on nondominant hand [47] and Adolescent Physical Activity Recall Questionnaire [48]	Change from preprogram to postprogram (after 14-week intervention)
Adolescent sedentary behavior	7-day 24-hour accelerometry, GENEActiv wrist-worn accelerometer [46] on nondominant hand [47] and Adolescent Sedentary Activity Questionnaire [49]	Change from preprogram (enrollment) to postprogram (immediately after a 14-week intervention)
Adolescent self-perception	Harter self-perception profile for adolescents [50]	Change from preprogram (enrollment) to postprogram (immediately after a 14-week intervention)
Parent and adolescent program satisfaction	Purpose-designed questionnaire	Postprogram (immediately after the 14-week intervention)
Parent and adolescent program satisfaction	Qualitative interviews	Postprogram

[a]BMIz: body mass index z-score.

Quantitative Evaluation: Outcomes

Program outcomes will be determined through pre-post program changes in lifestyle behaviors associated with increased cardiovascular risk and obesity (weight, diet, physical activity, and sedentary screen time) as well as changes in adolescent self-perception domains and overall self-esteem. Adolescents will be asked to complete online preprogram and postprogram semiquantitative surveys that assess key lifestyle behaviors. Self-reported adolescent height and weight will be used to calculate BMI z-score [43] and IOTF extended weight status categories [29]. Child diet will be measured by the Children's Dietary Questionnaire [44] and estimation of Serves of Core Foods [45], which will be compared with Australian Dietary Guidelines [31] and recommended serves of core and discretionary foods as per the Australian Guide to Healthy Eating [32]. Objective measurement of physical activity and sedentary time will be collected by 7-day 24-hour accelerometry, GENEActiv Original wrist-worn accelerometer [46] on nondominant hand [47]. Total time spent in sedentary, light, moderate, and physical activity will be explored. Additional activity data will be collected using the Adolescent Physical Activity Recall Questionnaire [48] and Adolescent Sedentary Activity Questionnaire [49]. Activity behaviors before and after the program will be compared with Australia's Physical Activity and Sedentary Behaviour Guidelines for Young People (aged 13-17 years) [30]. Self-perception and self-esteem will be collected using the Harter self-perception profile for adolescents [50]. This tool explores 8 specific self-concept domains: scholastic competence, athletic competence, social competence, physical appearance, behavioral conduct, close friendship, romantic appeal, and job competence, as well as a ninth subscale that reports global self-worth [51].

Quantitative Evaluation: Engagement and Program Satisfaction

Usage of the program will be measured using metrics, together with program satisfaction evaluation will inform adolescent engagement with the program elements and its acceptability. Data on program engagement for both parents and teens will be obtained from the online metrics collected by Moodle and Chatfuel, where applicable. Usage metrics will include weekly sessions viewed (n, %), total number of hits (n), average number of hits per week (n, %), number of individual sessions on Moodle (n), number of forum posts (n), and number of chatbot weekly check-ins completed (n, %).

Parent and adolescent satisfaction with the HOT program will be explored by a purpose-designed questionnaire that is distributed postprogram.

Quantitative Evaluation: Data Management and Analysis

Participants will be allocated unique identification (ID) numbers at enrollment, and all data collected will be recorded against this ID number; hence, evaluation data will be deidentified for research purposes. All questionnaires will be completed online through Qualtrics. The collection of evaluation data online has considerable advantages by avoiding manual data entry by research staff, minimizing data entry errors and staff time. Direct data entry also enables the research team immediate access to the data by downloading directly to IBM SPSS v23 (IBM Corp). As there is no control group for this healthy lifestyle intervention, preprogram and postprogram changes in lifestyle measures and child anthropometric data will be reported descriptively. Continuous data will be analyzed in SPSS and reported as means (95% CI lower limit to upper limit) or medians (interquartile range), as appropriate, and categorical data will be reported as n (%). Repeated-measures paired *t* tests will be used to analyze changes in outcomes over time for parametric data, whereas the Wilcoxon signed-rank test will be used for paired pre-post nonparametric data. The alpha value will be set at .05. The proportion of adolescents meeting recommendations for diet, physical activity, and sedentary time as per Australian Guidelines [30] before and after the program will also be described. Finally, associations between program engagement and participants' characteristics and program outcomes will be explored.

Qualitative Analysis: Data Collection and Analysis

On completion of HOT, parents and adolescents may be invited to participate in an interview or focus group to more deeply explore user experience in HOT. Qualitative semistructured interviews and/or focus groups will be conducted face-to-face for those living in the Adelaide area or over the phone for rural, remote, and interstate participants. Interview schedules will broadly aim to explore the user experience and usefulness of HOT for both adolescents and their parents. Interview questions will probe experiences for adolescents and their parents and will aim to capture what participants were seeking when they enrolled into HOT (including perception of lifestyle problems and their severity), what changes they have made to their lifestyle as a result of participating in HOT, what challenges to making behavior changes were encountered when participating in HOT, and what additional content and/or support would have helped to get more out of the HOT program, including to make suggested lifestyle behavior changes. A more detailed indicative interview schedule is presented in Table 4. It is anticipated that these participant interviews will elucidate suggestions for improvement of HOT, including HOT content and program delivery to optimize user's experience and satisfaction.

Qualitative semistructured interviews and/or focus groups will be audio-recorded and transcribed verbatim. Data will be entered and coded in NVivo version 10 qualitative data analysis software (QSR International Pty Ltd) and analyzed thematically. All data, including qualitative data, will be deidentified and stored in a secure, password-protected drive with access only available to the research team members.

Table 4. Indicative questions for parents and adolescents following participation in Health Online for Teens (HOT).

Domain	Questions for parents	Questions for adolescents
Introduction	Can you tell me a bit about yourself and your family?; How would you describe your relationship with [*adolescent name*]?; How would you describe your family lifestyle? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing)	Can you tell me a bit about yourself and your family?; How would you describe your relationship with your parent/s? Siblings?; How would you describe your family lifestyle? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing)
Motivations for enrollment	Can you tell me a little bit about how you became involved in HOT? (prompt: whose idea was it to be involved; how did you feel); Can you tell me about what you expected HOT to be like?; What was [*adolescent name*] hoping to get from HOT?; Can you tell me about [*adolescent name*]'s health?	Can you tell me a little bit about how you became involved in HOT?; Can you tell me about what you expected HOT to be like?; What were you hoping to get from HOT?; Can you tell me about your health?
Lifestyle changes	How motivated do you think [*adolescent name*] was to make changes during HOT?; How would you describe [*adolescent name*]'s lifestyle before HOT? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing); Do you think that there have been changes to [*adolescent name*]'s lifestyle during HOT? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing); Can you tell me how HOT has impacted your family lifestyle? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing); Follow-up probing questions related to making changes: Were there things which helped you to make these changes? Were there any things which made it harder for you to make the changes you wanted?	Can you tell me about your motivation to make changes during HOT? How would you describe your lifestyle before HOT? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing); Can you tell me about your lifestyle now? (prompts for lifestyle behaviors: diet, physical activity, sedentary behavior, sleep, wellbeing); Follow-up probing questions related to making changes: Were there things which helped you to make these changes? Were there any things which made it harder for you to make the changes you wanted?
Influences	Can you tell me who you think [*adolescent name*] looks to for healthy lifestyle advice?	Can you tell me where you go to get healthy lifestyle advice? (prompt: role models)
Parent role	What do you think your role was in HOT?; What are some examples of how you helped support [*adolescent name*] during HOT?; Can you describe to me what you think a parent's role is in their teenagers' health?	Can you tell me about the role of your parent in HOT?; Can you describe to me what you think a parent's role is in their teenagers' health?
Experiences with HOT	How would you describe your experience with HOT?; What are some of the things you liked about HOT? (prompt: and what about for [*adolescent name*]); What are some of the things you didn't like about HOT? (prompt: and what about for [*adolescent name*])	How would you describe your experience with HOT?; What are some of the things you liked about HOT?; What are some of the things you didn't like about HOT?
Time spent on HOT	Can you tell me a bit about how and when you used HOT?; Are there any suggestions for changes to HOT which would have improved the program for you? (prompt: and what about for [*adolescent name*]); Are there additional supports which would have helped you in HOT? (prompt: and what about for [*adolescent name*])	Can you tell me a bit about how and when you used HOT?; Are there any suggestions for changes to HOT which would have improved the program for you?; Are there additional supports which would have helped you in HOT? (prompt: and what about for [*adolescent name*])

Project Governance

The authors of this paper comprise the multidisciplinary steering committee for the project that includes an advanced accredited practicing dietitian, accredited practicing dietitians, a registered nutritionist, a physiotherapist, and health psychology and digital health experts. The project governance will also comprise a 4-member Expert Advisory Committee comprising the HOT project manager including 3 Australian experts in the areas of nutrition and dietetics, physical activity, and electronic health and behavior change and are external to the administering institution. Any publications arising from this study will be reviewed by all members of the steering committee before submission, and authorship will be decided according to contribution.

Results

Data collection for this study is ongoing. To date, 35 adolescents and their parents have participated in one of 3 groups.

Discussion

Multiple health risk behaviors are recognized to emerge and cluster during the adolescent life stage, including cigarette smoking, alcohol consumption, and drug use [52]. Although there are laws and public health strategies to address these behaviors in Australia, there is a lack of community programs and support for overweight or obese teenagers to make well-informed lifestyle decisions. Unlike younger children whom have had greater improvements in health over the past 50 years, teens are a comparatively underserved community

group [53]. This project is a pilot feasibility study of a new, innovative, evidence-based approach to address the public health priority of adolescent obesity, which aligns with recommendations from the World Health Organization Commission on Ending Childhood Obesity to provide family-based, multicomponent, lifestyle weight management services for children and young people who are obese as part of universal child health care [54]. It is crucial to intervene and increase healthy lifestyle behaviors during the teenage years to prevent irreversible cardiovascular damage [20] and minimize heart health risks.

Adolescent obesity remains a public health concern in Australia and many other Western nations. This study aims to explore the feasibility of the new online program HOT that promotes lifestyle behavior change for adolescents who are above a healthy weight. If this program is deemed to be feasible and acceptable for adolescents and their parents, program effectiveness will be explored in a subsequent randomized controlled trial. It is important to note that while preliminary pre-post outcome measures will be collected in this sample, these data will be used to inform sample size calculations for a larger randomized controlled trial rather than implying intervention effectiveness. Feedback from users will be incorporated in future intervention delivery where possible to improve the experience of future users.

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Authors' Contributions

MDM, AM, JM, and CJM conceived the study and were awarded competitive funding. All authors were involved in the design of the HOT program and its content. MDM is the chief investigator of the study. CJM is the project manager and has managed program development, ethics, study recruitment, implementation, and evaluation. CJM wrote the first draft of the paper, and all authors provided critical input and revised publication drafts. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist and items.
[PDF File (Adobe PDF File), 189 KB - resprot_v8i10e13340_app1.pdf]

Multimedia Appendix 2
Information sheet for teens and parents, consent form for teens and parents, assent form for teens.
[PDF File (Adobe PDF File), 209 KB - resprot_v8i10e13340_app2.pdf]

Multimedia Appendix 3
Schedule of enrolment, interventions, and assessments (SPIRIT template).
[PDF File (Adobe PDF File), 115 KB - resprot_v8i10e13340_app3.pdf]

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Abbreviations

BMI: body mass index
HOT: Health Online for Teens
ID: identification
IOTF: International Obesity Task Force
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Original Paper

Health Research Using Facebook to Identify and Recruit Pregnant Women Who Use Electronic Cigarettes: Internet-Based Nonrandomized Pilot Study

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Abstract

Background: Participant recruitment is often a challenge, particularly enrolling individuals with relatively rare characteristics. The wide reach of social media may provide a mechanism to overcome these challenges.

Objective: This paper aimed to provide information to researchers who seek to recruit participants from rare populations using social media for studies with demanding protocols. We aimed to describe a pilot study protocol that identified and enrolled pregnant women (second or third trimester) who were exclusive users of electronic cigarettes (e-cigarettes). We have described the recruitment methods, time, and cost; examined advertisement types that were more or less successful; discussed participant retention and relationship management; and described the process of collecting biological data.

Methods: In an open-access, nonrandomized pilot study, we placed Facebook advertisements that were selectively targeting women who were likely to be pregnant and interested in e-cigarettes or vaping. The advertisements invited individuals to complete a fully automated eligibility screener based on Qualtrics. Eligible participants were asked to (1) complete a Web-based survey that collected detailed information on the use of e-cigarettes, including the exact type of device and electronic liquid, (2) report the frequency and intensity of e-cigarette use for 3 months before pregnancy and during each trimester, and (3) provide a saliva specimen for a nicotine biomarker assay. We collected a photograph of each participant's e-cigarette device, 8 weeks after the mother's due date, to allow corroboration of the self-report and the baby's birth weight and gestational age from the participant's physician.

Results: Participants were recruited between August 19 and October 26, 2017. We enrolled 20 participants in 2 months at a cost of US $3421.28. Baseline data were collected for all 20 participants. Of the 20 women enrolled, 16 provided a saliva sample, 4 provided a photo of the e-cigarette device, and 10 provided physician contact information. Of the 10 physicians contacted by mail, 6 responded with information on the participants and their babies.

Conclusions: Study findings suggest that Facebook's targeting criteria should focus on e-cigarette users to maximize advertisement exposure of potentially eligible women. In addition, saliva sample collection was feasible among pregnant women (second or third trimester) who were exclusive e-cigarette users, but obtaining photographs and physician reports was problematic and called for further refinement. These lessons are likely useful to others who are seeking to use social media to recruit participants from rare populations into studies with demanding protocols.

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KEYWORDS

e-cigarette; pregnancy; social media

Introduction

Background

Participant recruitment is a challenge in public health research, particularly when the study aims to enroll those who are difficult to reach or recruit into research studies [1,2]. The population of interest may be rare among the overall population (eg, cystic fibrosis, Huntington disease, or Duchenne muscular dystrophy), difficult to identify or contact (eg, sex workers), or hesitant to participate because of stigma or legality (eg, people with substance use disorders, abuse victims, or illegal immigrants) [3-5]. To obtain a sufficient number of hard-to-reach participants, a researcher could conduct multicenter trials, but this can be quite expensive. An approach that has been increasingly used to address this challenge is to utilize social media to recruit from the larger population.

Social recruitment of study participants using Facebook has gained significant traction in recent years [6-8]. According to Pew Research Center's survey in 2018, about 80% of US adults aged 18 to 49 years use Facebook [9]. Facebook enables researchers to place targeted advertisements to reach populations with certain sociodemographic attributes (eg, age, sex, ethnicity, and location) and who communicate about their interests in a manner that makes them most likely to have the specific attributes needed for a given study. In addition, the platform enables individuals to enroll in a study by simply clicking on an advertisement and then being directed to the study site. Facebook recruitment has been successfully employed in recruiting tobacco users [10], substance abusers [6], and those suffering from depression [7]. The nascent literature on recruitment of electronic cigarette (e-cigarette) users using social media (eg, Facebook and Twitter), conducted by our team [11] and others [12], has shown promising results. However, the previous research solely relied on self-report measures to assess relevant variables (eg, e-cigarette usage and pregnancy status). A more rigorous approach requires corroboration of survey reports with objective evidence.

Objectives

Thus, the aim of this study was to examine the utility of Facebook to recruit pregnant women who used e-cigarettes into a study with a protocol that required acquisition of saliva samples, extensive surveys assessing details of e-cigarette use (20-30 min), photographs of the e-cigarette device, and physician corroboration regarding the pregnancy and infant. This pilot study was intended to inform us for developing a large study (>1000 pregnant e-cigarette users) to evaluate the effect of pregnant mothers' e-cigarette usage on infant health outcomes, primarily birth weight and risk of preterm birth. One predictable challenge was the ability to identify and recruit a sufficient number of participants. According to nationally representative data on both tobacco products and e-cigarette use during pregnancy, 4.9% of pregnant women were estimated to have used e-cigarettes from 2013 to 2014 [13]. The prevalence of e-cigarette use was much greater among current tobacco smokers (28.5%) but also included a sizable proportion of former smokers who switched to become exclusive e-cigarette users (prevalence of 2.3%). Thus, enrolling over 1000 pregnant women who used e-cigarettes exclusively and not in addition to tobacco—that is, minimum power to detect a potentially subtle effect of e-cigarette use on prenatal health for the larger study that will be informed by this pilot study—is unlikely to be feasible when the study is conducted at a single research site. Besides, recruiting pregnant women who use e-cigarettes into research studies may be difficult because of the stigma associated with risky behaviors during pregnancy, which can be reduced when the study is primarily conducted on the Web without the need to communicate directly with an interviewer and remain somewhat anonymous. These factors motivated this study to test the feasibility of employing Facebook recruitment. We conducted a pilot study to develop methods for an internet-based study of the effect of e-cigarettes on pregnancy outcomes, requiring recruitment of exclusive e-cigarette users in the second or third trimester of pregnancy. This study reports on recruitment methods, time, and cost, examines advertisement types that were more or less successful, discusses participant retention and relationship management, and describes the process of collecting biospecimens from participants. The lessons learned from our experience are likely useful to others who are seeking to use social media to recruit populations that are difficult to reach for studies with equally demanding protocols.

Methods

Ethics Approval and Consent to Participate

The Institutional Review Board of Brown University has approved the procedures presented in this paper. All participants were required to provide informed consent to participate in this study.

Overview

This study was an open-access (ie, participants self-enroll), nonrandomized pilot study. With regard to human involvement, advertisement, screening, and enrollment in the study was purely Web-based, and once enrolled, the research assistant contacted the participants only via email and there were no on-site visits. We used Facebook to recruit 20 women who were in their second or third trimester of pregnancy and used e-cigarettes but not tobacco. Our initial plan was to enroll 30 participants and determine how many we were able to retain throughout the study. Participants were recruited between August 19 and October 26, 2017. The recruitment ceased after exhausting the allocated predetermined budget. To our knowledge, there were no critical secular events (eg, significant changes in the available internet resources) during this period. The Facebook advertising tool placed messages in their feed selectively to target women who were likely to be pregnant and interested in e-cigarettes or vaping. The advertisement invited them to complete a Web-based eligibility-screening questionnaire. Inclusion criteria for this study were as follows: (1) pregnant women who were

in their second or third trimester, (2) aged 18 to 50 years, (3) currently a nonsmoker of tobacco, and (4) an e-cigarette user (≥5 days per week). The 5-day cut off point for the e-cigarette user was selected to minimize the variation in e-cigarette usage and in an effort to ensure that it was prevalent enough to have a meaningful effect on typical nicotine levels. After completing a screening survey, eligible participants were asked to read the consent form and complete the baseline questionnaire. Finally, each participant was asked to provide contact information to enroll in the study.

The survey instrument collected detailed information on (1) the exact type of e-cigarette device and electronic liquid used and (2) the frequency and intensity of use for 3 months before pregnancy and during each trimester of pregnancy. We requested a photograph of each participant's e-cigarette device, 8 weeks after the baby's due date, to allow corroboration of the self-report and the baby's birth weight and gestational age from the mother's physician.

Facebook Recruitment

To identify and recruit currently pregnant women who use e-cigarettes exclusively, we employed Facebook's advertisement tool from its suite of business user services. One of the advantages of recruiting on Facebook or other social media platforms is that the platform uses a *pixel* code—a short programming script that is placed on an advertiser's website to track traffic conversions from the platform's advertisements [14]. The pixel code allows Facebook's algorithm to characterize users who interact with an advertisement (eg, like, share, or directly click the post) and then further disseminate the advertisement to other Facebook users with similar characteristics. To ensure tracking all conversions with the Facebook pixel in advertisements, (1) click *Show Advanced Options* under Ads in Ads Manager; (2) check *Track all conversions from my Facebook pixel*; (3) click Save and Close; (4) apply to all campaigns if not default tracking with Facebook pixel.

We first used a *conversion tracking* advertisement and later used a *traffic tracking* advertisement [15,16]. Although both methods use Facebook pixel to gather information from Facebook users, they target slightly different groups. Conversion tracking gathers information from only those who end up at the final Web page (eg, those who purchase an item, sign up for a study, or provide contact information). On the other hand, traffic tracking gathers information from those who click through the processes (eg, an advertisement, screener, study explanation, or baseline questionnaire). As an analogy, on a clothing store website, conversion tracking would collect customer information from only those who purchased clothing, whereas traffic tracking would collect customer information from those who did not purchase any clothing but showed significant interest in certain items such as viewing it or adding it to their cart.

In this study, this screening process—from clicking the Facebook advertisement to providing contact information to complete enrollment in the study—took about 20 to 30 min. In this case, conversion tracking gathered information only from Facebook users who provided their contact information on the last page. Traffic tracking, on the contrary, allowed the algorithm to use specific demographic characteristics of Facebook users who spent a significant amount of time on activities leading up to the final Web page even if they did not complete the enrollment process. For the first 8 advertisements shown in Figure 1, we used conversion tracking that was used successfully by our group in the past [11] but was not as successful in another study recruiting smokers [10].

Figure 1. Facebook advertisements.

After employing the 8 advertisement sets (Ad sets) using conversion tracking, we contacted the Facebook marketing consultant (known as a marketing expert) because of the low screening rate. Through phone meetings and emails, the Facebook consultant helped us understand how to optimize current campaigns, but this service was provided only for a 28-day period. The consultant suggested we use traffic tracking instead of conversion tracking. The suggestion was motivated by the fact that the screening process of this study is similar to a process (ie, ideal for traffic tracking) than to a snapshot decision (ie, ideal for conversion tracking). An integral metric to determine the cost-effectiveness of conversion versus traffic is *cost per results*, which can be found in the summary table provided in Facebook Ads Manager. Cost per results counts the number of results (eg, conversion or traffic) a researcher received based on the settings for the advertisement. For example, if a researcher selected conversions as their campaign objective, the results metric may show the number of *View*

Contents that occurred because of someone seeing their advertisement. In this study, for conversion, the cost per results was *View Contents*. For traffic, the cost per result was *Link Clicks*.

Data Collection From Participants

After clicking on the advertisement, participants were first screened to see if they were eligible for the study. Eligible participants were then asked to do the following:

1. Complete an enrollment questionnaire on the Web that included their demographic background, history of e-cigarette and tobacco use, and current e-cigarette use.
2. Complete a detailed 3-day diary of e-cigarette use, receive a saliva collection kit via mail, and mail back a saliva sample that was assayed for the nicotine metabolite, cotinine, as an indicator of the level of recent nicotine exposure.
3. Provide pictures of the e-cigarette device by uploading digital photos via a Dropbox link embedded in the survey.
4. After giving birth, complete a follow-up questionnaire to update e-cigarette use information for the later period of pregnancy and report on the outcome of the pregnancy.
5. Grant permission to obtain the information on the birth outcome from the participant's doctor to verify the birth weight and gestational age.

All surveys were conducted on the Web using the Qualtrics platform [17]. To compensate participants for their time, we provided Amazon's electronic gift cards as incentives at each stage of the process: enrollment (US $10), completing the 3-day e-cigarette diary and providing a saliva specimen (US $25), completing the follow-up questionnaire and providing consent to review birth records after delivery (US $10), and a bonus for those who completed all 3 parts (US $15). We did not specify a period for participants in which they should submit the aforementioned data to obtain incentives. Safety and security procedures were elaborated in the informed consent form, which was collected on the Web via Qualtrics. With regard to harms or unintended effects, we noted the following:

> *the only risk to you of participating would be if personal information about you or your baby reached people other than the researchers. We will be extremely careful to do everything we can to make sure that doesn't happen. Your data will be stored on a computer at the Brown University, never on a laptop or memory stick. The data will only be seen by people on the research team who need to work with it or the Brown Institutional Review Board overseeing the study. There are no direct benefits to you from being in the study. However, you may be contributing to research that will help us provide more accurate information about e-cigarettes and health to expectant mothers in the future.*

Data Collection From Physicians

Although self-report is known to be accurate for birth weight and very good (but not perfect) for gestational age [18], it is important to maximize accuracy, as we were interested in potentially subtle effects of e-cigarette use on pregnancy outcome. Birth records use both the last normal menstrual period and a clinical estimate as a means of assigning gestational age at delivery. As the clinical estimate reflects all the information available to the clinician, most importantly ultrasound, it has been shown to be the more accurate approach than relying on reporting of the last menstrual period to calculate gestational age at delivery [19]. Although birth records are a more accurate measure, whether it can be obtained successfully in clinical trial is unknown, and thus, this study attempted to test its feasibility. Toward this end, we contacted participants and asked permission to obtain birth outcome information from their doctors 8 weeks after the baby's due date. Then, we contacted physicians to request the baby's health information by mail or fax. Physicians were informed that the mother had provided written consent to share this information. To facilitate the process, we inserted a preaddressed envelope with a stamp. If a physician did not reply within 2 weeks, research staff contacted the physician's office via phone.

Results

Facebook Recruitment

Using Facebook, we were able to identify and enroll 20 participants in a 2-month period. Using conversion tracking, we launched 8 Ad sets sequentially from August 19 to September 13, 2017 (Table 1).

Table 1. Conversion per Facebook advertisement specifications and enrollment outcome.

Advertisement set (Ad set)	Daily spend (US $)	Duration (days)	Number of advertisements	Conversion window (day)	Total cost (US $)	Total enrolled	Total screened
Ad set 1	200.00	6	3	7	829.86	5	306
Ad set 2	200.00	3	3	7	162.52	1	51
Ad set 3	200.00	3	2	7	741.66	5	228
Ad set 4	200.00	3	3	7	599.32	4	51
Ad set 5	300.00	3	3	7	598.93	3	170
Ad set 6	150.00	3	1	1	448.91	0	89
Ad set 7	150.00	2	1	1	298.60	0	82
Ad set 8	150.00	2	1	1	299.95	1	172

We incrementally fine-tuned our parameters for the subsequent set based on the turnout of the ongoing set. The specifics of daily budget and audience details were informed by our team's previous research [11]. Ad sets 1 and 2 used the same search terms, which included *electronic cigarettes*, *vapor*, and *pregnancy*, and enrolled 5 participants. As many people were screening out from Ad set 1, we added *baby shower* and *new moms* to the existing search terms in Ad sets 3 and 4 and enrolled an additional 9 participants. This may have influenced the reduction in per enrollment cost from approximately US $165 (Ad sets 1 and 2) to US $150 (Ad sets 3 and 4). In Ad set 5, we increased the daily money spent to US $300 (from US $200) and enrolled an additional 3 participants, but this resulted in a higher per enrollment cost of approximately US $200. In Ad set 6, daily money spent was reduced to US $150; the number of advertisements within an Ad set was reduced from 3 to 1; and conversion window was reduced to 1 day from 7 days. However, Ad set 6 enrolled no participants. In Ad set 7, we expanded age restriction from 18-25 to 18-50 but enrolled no additional participants. In Ad set 8, we moved up the conversion to screeners from the final Web page but this only resulted in enrolling one additional participant.

In this study, for conversion, the cost per results was *View Contents*, which ranged from US $17.64 to US $741.66. For traffic, the cost per result was *Link Clicks*, and the cost was significantly lower, which ranged from US $1.61 to US $3.07. When interpreting the performance of each Ad set, we could not conclude that the later sets (Ad set 3-7) with new features were ineffective. Ad sets were not run independently, even if they ran separately, thereby it is critical to understand that the subsequent Ad sets used pixel information from the previous sets. In fact, the new sets still let our team deliver the advertisement to the same group of Facebook users, and it is likely that we simply exhausted the pool of potential participants with the limited budget allocated to the advertisements. In essence, repeated exposure of the advertisement may not have yielded much more enrollment because those interested in the study had already clicked the advertisements and completed the screener.

Using traffic tracking, we launched 2 Ad sets from October 12 to October 26, 2017 (Table 2).

As we had been using pixel from Ad sets 1 to 8, our pixel had accumulated information regarding the participants who enrolled in our study. With this pixel, we created a *targeted audience*. This *targeted audience* was considered too specific according to the Facebook platform and estimated daily results indicated that the traffic advertisement could reach about 16 to 40 individuals. Perhaps, because of this very narrow target, the rate of enrollment was slow as we enrolled 5 participants in 10 days. However, considering that we only spent US $27.64, we observed a remarkable reduction in per enrollment cost from US $150 to US $250 to US $4.60 per participant. These new Ad sets appear to constitute a better target pool given how the pixels track more information from site interaction. Perhaps, because of this, the traffic tracking advertisements were delivered to a new audience not included in the previous 8 sets that employed conversion tracking.

The flow diagram of Facebook advertisement clicks (N=3891) to final enrollment (n=20) is illustrated in Figure 2. Of 3891 Facebook users who clicked the advertisement, 34.67% (1349/3891) completed the screener. Among the 1349 participants who completed the screener, only 3.48% (47/1349) met the eligibility criteria. Among 1349 participants who completed the screener, 6.82% (92/1349) were dual users, 5.34% (72/1349) used tobacco only, 7.78% (105/1349) used e-cigarettes only, and 58.86% (794/1349) used neither tobacco nor e-cigarettes. Among the 197 e-cigarette users, 49.7% (98/197) were ineligible because of low frequency of e-cigarette use (<5 days per week). Most who completed the screener (93.92%, 1267/1349) were pregnant, 59 (4.37%, 59/1349) were not pregnant, and 23 were (1.70%, 23/1349) missing. Among those completing the screener, 1051 (77.91%, 1051/1349) were in their second or third trimester, 211 (15.64%, 211/1349) were in their first trimester, and 87 (6.45%, 87/1349) did not indicate a trimester. Taken altogether, there were 47 survey respondents, who simultaneously met all of the inclusion criteria who were then directed to the second page, *Informed Consent*, and almost all did so (97%, 46/47) with 78% (36/47) going on to complete the intake interview.

Demographic characteristics of the enrolled participants are shown in Table 3.

The enrolled participants likely had a high literacy level considering that 65% of the participants were at least *some college* or above. On average, participants were about 22 years old (mean 21.6, *SD* 2.0), with prepregnancy body mass index placing them in the overweight to obese category (mean 29.6, *SD* 6.8). On the basis of the survey about participants' past tobacco use, 9 (36%, 9/25) smoked regular cigarettes before using e-cigarettes, 9 (36%, 9/25) used a vaping device to try to quit smoking completely, and 11 (44%, 11/25) smoked regular cigarettes before using e-cigarettes. e-cigarette: electronic cigarette

Table 2. Traffic per Facebook advertisement specifications and enrollment outcome.

Advertisement set (Ad set)	Lifetime spend (US $)	Duration (days)	Number of advertisements	Total cost (US $)	Total enrolled	Total screened
Ad set 9	1000.00	11	1	27.63	5	9
Ad set 10	1000.00	3	3	161.41	0	201

Figure 2. Flow diagram from the Facebook advertisements to enrollment. e-cigarette: electronic cigarette.

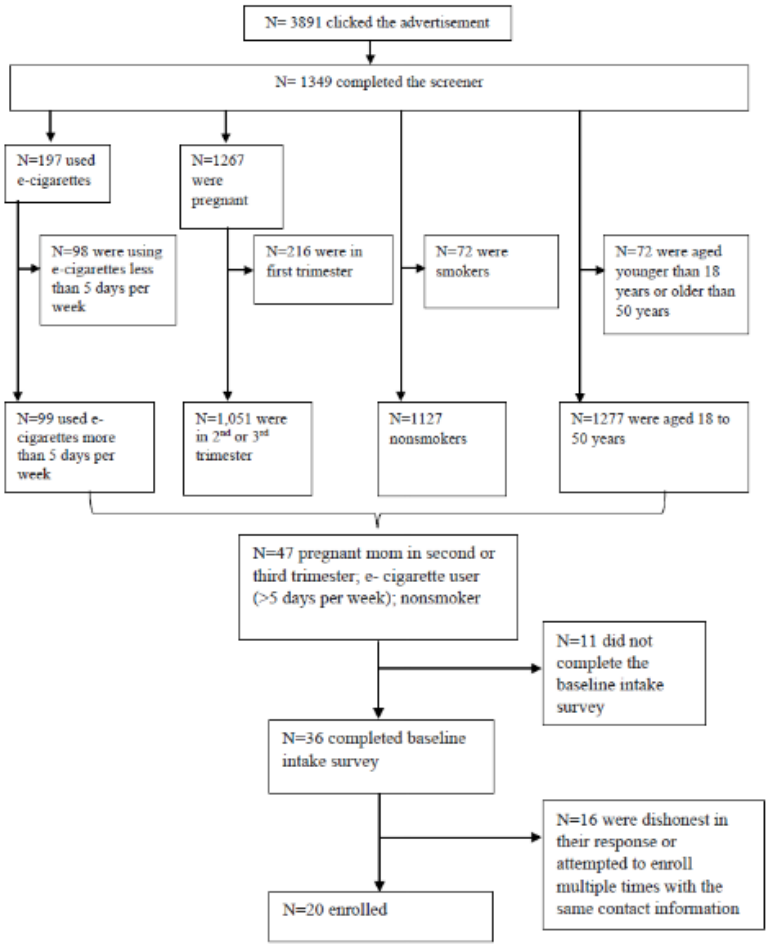

Table 3. Demographic characteristics (n=20).

Characteristics	Values
Age (years), mean (SD)	21.6 (2.0)
Prepregnancy body mass index (kg/m^2), mean (SD)	29.6 (6.8)
Education, n (%)	
High school graduate	6 (30)
Some college	9 (45)
College graduate	1 (5)
Postgraduate work	1 (5)
Do not know or prefer not to answer	3 (15)

Relationship Management

Studies that recruit participants via Facebook may elicit Facebook users' questions or complaints about the study. Negative posts may influence the recruitment process as prospective respondents can see the unfavorable comments and might avoid the advertisement. We responded to negative comments from a Facebook user who later enrolled in the study. This user posted a comment on one of the advertisements in the Ad set 3 (September 4-8), questioning the ethical basis for this research on the presumption that a pregnant woman's e-cigarettes usage would have a negative effect on the baby. We responded to the post explaining the scientific rationale and ethical ground of this research (Figure 3).

Figure 3. Addressing a negative comment from a Facebook user.

Participants were asked for a 3-day period in which they preferred to receive the saliva sample kit—between the day after the survey and mother's due date for her baby—and were asked to provide their address, name, and contact information. Once they submitted the survey, research staff provided a US $10 Amazon gift card via email. Among 36 participants, research staff excluded 16 participants (44%) who appeared to be dishonest in their responses, presumably to collect the incentive. For example, some participants attempted to enroll twice in the study using a different name but the same contact information. One participant claimed that she had not received the Amazon incentive after our research team had received an automated message from Amazon.com stating that she had redeemed her gift card. After these exclusions, we were able to retain 20 participants.

Subsequent Data Collection From Participants

Of the 20 women enrolled, we were able to obtain biospecimens from 16 participants (80%), and we were able to obtain a photo of the e-cigarette device from 4 participants. A total of 10 participants provided follow-up data including their physician's contact information. Of the 10 physicians contacted, 6 responded to our mail and provided follow-up information of the participant and the baby. Our team did not specify a period for participants in which they should submit the aforementioned data to obtain incentives.

Discussion

Principal Findings

Results from this study may help to inform strategies used to recruit pregnant women who use e-cigarettes but not tobacco into a study with a protocol that has multiple, demanding components. On the basis of the results of the Facebook advertisements, the lesson learned from this study regarding identifying rare populations was the importance of *targeting criteria*.

Although the advertisements recruited many pregnant mothers, it recruited few pregnant e-cigarette users. Specifically, among the 1349 participants who completed the screener, only 197 used e-cigarettes whereas almost all were pregnant. As we did not want to disclose our direct interest in e-cigarette usage because we were concerned that it could lead to false reporting to receive a financial incentive, the picture and text accompanying the advertisement did not imply that this was a focus of the research. In contrast, it was clear that the study was about pregnancy health based on the pictures and the title of the study (Figure 1). In this regard, the targeting criteria of Ad set parameters—which surreptitiously deliver the advertisements based on a Facebook user's profile and behaviors—perhaps should have solely focused on e-cigarette behavior while forgoing other parameters (eg, *pregnancy* or *new mom*) initially.

By doing so, we could have reached more e-cigarette users and then proceeded to seek those who were pregnant. The Facebook pixel function should be focused on the hardest-to-reach characteristics of the population.

A related lesson learned in this study is that a robust recruitment budget is needed to attain the desired number of participants. Simply put, a general principle of Facebook advertisements is that the more money advertisers allocate, the more people are exposed to the advertisement. Furthermore, the recruitment period must be sufficiently long to obtain the desired number of participants**.** We achieved the greatest success when allowing recruitment to remain open for weeks rather than days. This likely helps maximize the reach of the advertisement and allows the Facebook algorithm to place the advertisement in front of those that best match willing, eligible individuals. Considering the remarkable drop in the per enrollment cost from US $150 to US $250 to US $4.60 per participant, it seems reasonable to conclude that a reduced enrollment process benefitted solely from changing to traffic tracking from conversion tracking. However, while running the advertisements using conversion tracking for 3 weeks, the pixel accumulated extensive demographic information of the Facebook users who were exposed to our advertisements. With this pixel, later advertisements based on traffic tracking were able to expose the advertisements to those who were likely to enroll in this study. In other words, the remarkable drop in enrollment cost is likely attributed to both prolonged Facebook pixel exposure and choosing traffic tracking. Altogether, this suggests that the Facebook pixel could eventually identify the target population with a reasonable budget, a tracking system that suits the nature of enrollment process (ie, traffic vs conversion), and a sufficiently long recruitment period and the utility of the pixel. A third lesson learned is with regard to participant burden. We likely lost some participants because of the length of the intake assessment, which took approximately 15 to 20 min, as 10 eligible participants discontinued. In retrospect, providing a congratulatory message in the process of the survey may have been an effective method to prolong participants' engagement with the survey. Finally, it may have been useful to obtain qualitative feedback at the end of the study.

On the contrary, the collection of biospecimens by mail was feasible as indicated by an 80% completion rate for the saliva samples (16 samples out of 20 participants). Of note, this may be generalizable to a study protocol that enrolls participant who demonstrate a certain level of commitment toward the study (eg, 20-30 min of intake survey). Saliva samples can be a rich source of biological information, and such objective assessments of individual traits can vastly enhance the scientific rigor of an internet-based study. It should be noted that only biomarkers that do not require supervised collection and are stable at room temperature can readily be incorporated into an internet-based study, and cotinine meets all of these criteria. Collecting photos via Dropbox was not as successful, as we obtained photos from only 20% of the participants. A possible explanation of this low rate is that many e-cigarette users may not have the vaping device any longer, as many may tend to quit tobacco use or go back to combustible cigarettes after delivering the baby. A more integrated survey approach in which users attach the photo directly to the survey may be less burdensome and more successful. Finally, collecting the baby's health information from the physicians was challenging as we only obtained 60% of the physicians' responses. Each of these components calls for evaluation of the study's burden, financial incentives, and privacy considerations.

Limitations

It is worth noting the possibility of sampling bias such that Facebook users may not be representative of the general population. A systematic review of this topic suggests that Facebook-recruited samples were generally representative of samples recruited through traditional methods, except that the socioeconomic status was higher among Facebook users [20]. Higher socioeconomic status among Facebook users has been also highlighted by a study that examined the representativeness of social media in Great Britain [21]. In addition, the requirements to read the consent form on the Web and complete questionnaires on the Web suggest that a relatively high literacy level, as well as high *internet literacy*, would be required for participation. Altogether, this study may have recruited those with a higher education level than the general population. Finally, to the extent of our knowledge, a Facebook Ad user has no insight into Facebook's placement of advertisements under either traffic or conversion tracking. As such, it is impossible to evaluate the potential for bias beyond our initial target criteria. As with other types of quota sampling, conversion or traffic tracking strategies monitor the returns as they come in, which allows a researcher to promptly modify the recruitment criteria to optimize the sampling bias.

Conclusions

Our study suggests that researchers focus the Facebook Ad set parameters to the hardest-to-reach features of the population (ie, e-cigarette usage) with other desired attributes apparent in the advertisements. It is essential to allocate a robust budget and provide an extended recruitment period for each Ad set. Researchers should minimize participant burden in the recruitment process to maximize enrollment and prepare responses or a Frequently Asked Questions document for participant retention and relationship management. Finally, saliva sample collection for cotinine analysis or other assays is feasible with careful attention to minimizing participant burden and providing the right incentive. More effort would be needed to determine how best to obtain better success in collecting photos and health information from physicians. These lessons are likely useful to others who are seeking to use social media to recruit participants who are rare in the population into studies with demanding protocols.

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Authors' Contributions

DAS and JWT designed the study. YPH and JM reviewed the study design with regard to Facebook recruitment. HHL conducted the study and drafted the manuscript. All coauthors reviewed the design and manuscript. All authors have contributed to and have approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 2626 KB - resprot_v8i10e12444_app1.pdf]

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Abbreviations

Ad sets: advertisement sets
e-cigarette: electronic cigarette

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Protocol

Improving the Health of Individuals With Cerebral Palsy: Protocol for the Multidisciplinary Research Program MOVING ON WITH CP

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Abstract

Background: Cerebral palsy (CP) is one of the most common early onset disabilities globally. The causative brain damage in CP is nonprogressive, yet secondary conditions develop and worsen over time. Individuals with CP in Sweden and most of the Nordic countries are systematically followed in the national registry and follow-up program entitled the Cerebral Palsy Follow-Up Program (CPUP). CPUP has improved certain aspects of health care for individuals with CP and strengthened collaboration among professionals. However, there are still issues to resolve regarding health care for this specific population.

Objective: The overall objectives of the research program MOVING ON WITH CP are to (1) improve the health care processes and delivery models; (2) develop, implement, and evaluate real-life solutions for Swedish health care provision; and (3) evaluate existing health care and social insurance benefit programs and processes in the context of CP.

Methods: MOVING ON WITH CP comprises 9 projects within 3 themes. Evaluation of Existing Health Care (Theme A) consists of registry studies where data from CPUP will be merged with national official health databases, complemented by survey and interview data. In Equality in Health Care and Social Insurance (Theme B), mixed methods studies and registry studies will be complemented with focus group interviews to inform the development of new processes to apply for benefits. In New Solutions and Processes in Health Care Provision (Theme C), an eHealth (electronic health) procedure will be developed and tested to facilitate access to specialized health care, and equipment that improves the assessment of movement activity in individuals with CP will be developed.

Results: The individual projects are currently being planned and will begin shortly. Feedback from users has been integrated. Ethics board approvals have been obtained.

Conclusions: In this 6-year multidisciplinary program, professionals from the fields of medicine, social sciences, health sciences, and engineering, in collaboration with individuals with CP and their families, will evaluate existing health care, create conditions for a more equal health care, and develop new technologies to improve the health care management of people with CP.

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KEYWORDS

cerebral palsy; health care; pain; health; disability; multidisciplinary

Introduction

Background

All children should have the right to health and quality of life [1], yet children with disabilities have impairments, putting them at risk for reduced participation, limited involvement in everyday activities, and reduced quality of life [2,3]. Cerebral palsy (CP) is one of the most common early onset disabilities with a prevalence of 2 to 3 per 1000 live births [4,5]. Males are marginally overrepresented but there are no known sex differences in gross motor function [6,7]. The brain damage that causes CP is nonprogressive, but associated secondary conditions, by definition preventable [8], develop and deteriorate over time. Levels of function and types of comorbidities and secondary conditions vary greatly, and physical and occupational therapy, orthoses, medications, and a range of orthopedic surgeries are used to maximize physical function.

Since 1994, children and adolescents with CP in the southern regions of Sweden have been systematically enrolled in a follow-up program called the Cerebral Palsy Follow-Up Program (CPUP). By 2007, more than 95% of all youths with CP born in 2000 or later in all health care regions of Sweden were enrolled, and the program started receiving government funding and became a national quality registry. CPUP or adapted versions of it have been implemented in Norway, Denmark, Iceland, Scotland, Jordan, and New South Wales in Australia [9]. Data are systematically collected on variables such as gross motor function, mobility, hand function, range of motion, degree of spasticity, hip displacement, pain, and scoliosis (see www.cpup.se for a complete list). More recently, adults with CP are eligible to participate; however, the adult cohort in CPUP does not comprise the total population.

CPUP has improved certain aspects of health care for individuals with CP and strengthened collaboration among professionals. For instance, the prevalence of hip dislocations in children with CP was reduced from approximately 10% to 0.5% in a time span of 10 years, and the number of orthopedic surgeries has been reduced [10,11]. However, there are still numerous health care–related issues to resolve. Taxpayer-funded universal health care should be evidence-based, or based on best practice if scientific evidence is lacking, and provided equitably to those who need it, yet educational level, geographical residence, sex, age, and country of origin are factors known to influence access to health care [12-14]. Research has pointed to sex differences in the treatment of children with CP; boys are more likely to receive botulinum toxin A [15] and undergo selective dorsal rhizotomy [16]. In northern Sweden, boys with CP have been reported to receive more physical therapy than girls [17]. The concepts of equality (ie, everybody receives the same, regardless of individual needs and outcomes) and equity (ie, fairness and equality in outcomes is of main interest, meaning not everybody receives the same) need to be considered in the context of treatment. Sex differences in treatment might be warranted if, for instance, biological differences between the sexes (eg, boys might hypothetically be more spastic) exist. We have not found support for such a hypothesis. If differences in treatment exist, it is important to know why and what the consequences are.

Approaches to address CP-related health care differ. In CPUP, the focus is on prevention. One goal, for example, is to prevent hip dislocations before they occur by monitoring and following the children over time. For a preventive approach to be successful, it is necessary to be able to predict who is at risk and in need of preventive treatment. As an example, CPUP data have been used to develop risk scores to predict hip displacement [18]. People who for various reasons do not stretch their muscles sufficiently during the day are at risk of developing contractures [19]. It would, therefore, be useful to be able to monitor the movement and range of joint motion pattern during longer periods to predict the risk of contracture development. In other countries (eg, Finland), a reactive health care approach is used instead, and surgery is performed after the hip dislocations have occurred.

To enable prevention-focused work requires early detection and receiving an accurate CP diagnosis. According to the CPUP guidelines, a pediatric neurologist or specialist with similar expertise should confirm or dismiss the CP diagnosis by the time the child is aged 4 to 5 years. A shortage of certain specialists, including pediatric neurologists, is a challenge in Sweden. The number of pediatric neurologists employed in the habilitation setting, where children with CP receive much of their health care, has decreased, while the workload has increased. Furthermore, the number of children in Sweden with a confirmed or dismissed diagnosis of CP, per current guidelines, has decreased. Currently, 30% of those old enough to have a confirmed diagnosis of CP reported in CPUP have not yet been diagnosed [20]. Furthermore, sparsely populated rural regions are often less attractive to professionals, and such regions might be prone to a chronic lack of professionals and specialists. Better use and implementation of existing technology is one possible solution to this. Videoconferencing, online examinations, and online prescription refills are commonplace. In the context of

CP, it is the process and implementation that need to be developed and evaluated, not the technology, per se. Engaging experienced pediatric neurologists long distance in diagnosing and treating individuals with CP within the CPUP framework is one possibility that will be explored and studied in this research program.

Pain is present already in young children with CP and increases with age [21-25], and researchers have cautioned that the pain is frequently not identified or that it is undertreated [23,24]. In spite of the decrease in hip dislocations [10], many who do not have dislocations still report pain in the hips [26]. One of the next challenges in Sweden is to develop a cost-effective pain prevention, reduction, and treatment program and implement it using the existing CPUP infrastructure. This requires knowledge of the pain panorama in individuals with CP.

Individuals with CP are at risk of experiencing cognitive difficulties. Although the degree of motor and cognitive impairment do correlate [27], there is no absolute correlation between motor and cognitive functioning [28,29]. Cognitive impairment can be found across the spectrum of severity of gross motor function, and it is warranted to assess all children with CP [30] and, arguably, adults. Nevertheless, cognition is often not assessed in this population [31] because of an assumption that children with CP cannot be cognitively assessed because of speech and motor impairments. However, research has shown that it is possible to assess 62% of children with CP with psychological tests in a standardized manner [29] and at least 80% if the mode of responding to the test questions is adapted (eg, pointing with eye-gaze instead of with a finger). Results from a cognitive assessment might indicate that assistive technologies are needed, that there is a need for augmentative and alternative communication (AAC), schools and work places can be informed in a timely manner, and appropriate expectations can be set. In addition, cognitive impairment needs to be considered when applying for social insurance and disability benefits.

In Sweden, children and youths with CP and certain other disabilities receive health care and treatment at habilitation centers free of charge. The multidisciplinary professionals at these centers are tasked with overseeing the overall health and development and providing the necessary health care for children with disabilities. Physicians working in habilitation centers spend a lot of time documenting and writing certificates to the Social Insurance Agency and local municipalities. These certificates serve as the basis for decisions regarding what benefits the children and their families are entitled to, how often, and how much. How social benefit claims are handled and decisions are made are burning political issues in Sweden. Many users with CP consider the benefit application haphazard and believe decisions are made based on geography, which physician completed the certificate, and who processed the claim.

Overall Purpose and Specific Aims

The objectives of the research program MOVING ON WITH CP are to (1) improve the health care processes and delivery models and thereby improve health, quality of life, and social participation in this population; (2) develop, implement, and evaluate real-life solutions for Swedish health care provision; and (3) evaluate existing health care and social insurance benefit programs and processes in the context of CP (Figure 1).

Figure 1. Research themes in MOVING ON WITH CP.

The specific aims are as follows:

- Evaluate the treatment effect, clinically and cost-effectively, of a population-based preventive approach (CPUP) compared to a reactive health care (regular care) approach (project A1)
- Investigate the prevalence, intensity, and specific body sites affected by pain and if this pain is related to demographic, socioeconomic, and disability factors (project A2)
- Investigate effects of pain on short- and long-term outcomes in relation to sleep, social participation, and labor market outcomes (project A2)
- Evaluate the implementation of the CPCognition (CPCog) protocol in Sweden and Norway (project A3)
- Determine what is relevant to study and report for adults with CP based on the International Classification of Functioning, Disability, and Health categories specific to CP (project A4)
- Study the effects of living with CP in terms of social participation and health and if the Swedish social insurance systems contribute to financial protection and enable acceptable living conditions (project B1)
- Determine if consequences of CP and access to formal societal support are equitably distributed based on disability and functional factors or if demographic and socioeconomic factors are related to access to societal support (projects B2 and B3)
- Develop, test, and evaluate a template based on structured and valid information on body functions from CPUP to be used by physicians in the certificate-writing process (project B3)

- Develop, test, and evaluate a device that continuously measures movement and range of joint motion (project C1)
- Develop, test, and evaluate an eHealth (electronic health) consultation service by tertiary care specialists using the infrastructures available through CPUP and MMCUP—the equivalent of CPUP but for individuals with a diagnosis of spina bifida (project C2)

Methods

Procedure and Data Sources

Summaries of the individual projects included in the program are presented in Multimedia Appendix 1 according to the three themes. Both quantitative and qualitative designs are included. The registry studies will be based on secondary analyses of preexisting data available in CPUP and general national registers (Statistics Sweden and the National Board of Health and Welfare). The data will be managed, analyzed, presented, and archived in compliance with national regulations, European Union directives (when applicable), Good Epidemiological Practice, and the requirements posed by the ethical review boards.

Ethical Considerations

The current research program consists of a number of different projects. For the research projects that are based on CPUP data, ethical approvals are already in place (LU 443-99, revised 2009, and LU EPN 2017/78). Additionally, ethics approvals for the Finnish cohort data (project A1: HUS/3640/2017, project C1: 2019-02452, and project A4: MEC-2018-1126) are in place. We are in the process of obtaining ethical approval for the remaining projects. No research will commence until the required approvals have been obtained.

Results

This is a protocol for a research program and there are no results to report to date. The program is funded by the Swedish Research Council for Health, Working Life, and Welfare. The CPUP User Board, which consists of individuals with CP and family members, has reviewed and provided feedback on the individual studies. The first results are expected to be available at the end of 2019, and scientific publications are expected to be forthcoming at the beginning of 2020.

Discussion

Summary

CP-related research has advanced during the last decades. Although we know more about the disability, there are numerous knowledge gaps and a number of health care delivery processes that could be improved. In MOVING ON WITH CP, we are addressing some of these knowledge gaps. Importantly, the program is multidisciplinary, and the research team consists of physicians, psychologists, public health scientists, physical therapists, health economists, and engineers. For research in general and applied research in particular, it is crucial to get the insights of those who are ultimately affected. In our case, that means individuals with CP and their families. By involving the CPUP User Board, we will ensure that the research we do and plan to do is actually relevant to the stakeholders. Moreover, the stakeholders can facilitate the knowledge brokerage by ensuring that the information to be communicated outside of the professional community is relevant and appropriate.

Research on disability can at times be hampered by small sample sizes. By using register-based research, it is possible to increase the statistical power while at the same time increasing the external generalizability and reducing selection bias. In CPUP, we have systematically followed individuals with CP for over two decades and we have longitudinal data available that enable us to evaluate a number of aspects in terms of health care and health care delivery. Moreover, through CPUP we also have the infrastructure in place to implement our findings as they become available. Contributing to the knowledge base is critical; however, an important purpose of MOVING ON WITH CP is to ensure that the health care of individuals with CP is evidence-based, up to date, cost effective, and fair. The type of health care received should not depend on a person's geographical location or sex.

In order to move health care management of CP forward, we must use the development that takes place in technology and collaborate with experts in these areas. We will collaborate with technical experts to create an organization that compensates for inequalities in access to health care and create technical equipment that improves the assessment of movement activity in people with CP. To implement the purpose of MOVING ON WITH CP, three themes have been developed and encompass all projects.

Limitations

There will be numerous limitations to the research program. However, these will be discussed in more detail as the results from the individual projects are reported.

Conclusion

The results of this research program will be of interest to many different research areas such as medicine, social sciences, political science, health economics, as well as the fields of inequality, disability, and biotech research. More importantly, the results will lead to tangible improvements in Swedish health care. The findings will be disseminated to a wide audience including stakeholders (individuals with CP, families, and governmental agencies); the general public; user organizations; higher education students; policy makers; health care administrators/providers; and the scientific community.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of the studies in MOVING ON WITH CP.
[PDF File (Adobe PDF File), 113 KB - resprot_v8i10e13883_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report from Forte.
[PDF File (Adobe PDF File), 84 KB - resprot_v8i10e13883_app2.pdf]

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Abbreviations

CP: cerebral palsy
CPCOG: Cerebral Palsy Cognition Module included in CPUP
CPUP: Cerebral Palsy Follow-Up Program
eHealth: electronic health
GMFCS: Gross Motor Function Classification System
ICF: International Classification of Functioning, Disability, and Health
MACS: Motor Ability Classification System
MMC: myelomeningocele
MMCUP: Myelomeningocele Follow-Up Program

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Protocol

Development of a Patient-Reported Outcome Instrument for Patients With Severe Lower Extremity Trauma (LIMB-Q): Protocol for a Multiphase Mixed Methods Study

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Abstract

Background: A current limitation in the care of patients with severe lower extremity traumatic injuries is the lack of a rigorously developed patient-reported outcome (PRO) instrument specific to lower extremity trauma patients.

Objective: This mixed methods protocol aims to describe phases I and II of the development of a PRO instrument for lower extremity trauma patients, following international PRO development guidelines.

Methods: The phase I study follows an interpretive description approach. Development of the PRO instrument begins with identifying the concepts that are important to patients, after which a preliminary conceptual framework is devised from a systematic literature review and used to generate an interview guide. Patients aged 18 years or above with limb-threatening lower extremity traumatic injuries resulting in reconstruction, amputation, or amputation after failed reconstruction will be recruited. The subjects will participate in semistructured, in-depth qualitative interviews to identify all important concepts of interest. The qualitative interview data will be coded with top-level domains, themes, and subthemes. The codes will then be utilized to refine the conceptual framework and generate preliminary items and a set of scales. The preliminary scales will be further refined via a process of conducting cognitive debriefing interviews with lower extremity trauma patients and soliciting expert opinions. Phase III will include a large-scale field test, using Rasch measurement theory to analyze the psychometric properties of the instrument; shortening and finalizing the scales; and determining the reliability, validity, and responsiveness of the instrument.

Results: Phases I and II of this study have been funded. Phase I of this study has been completed, and phase II began in January 2019 and is expected to be completed in November 2019. Phase III will begin following the completion of phase II.

Conclusions: This protocol describes the initial phases of development of a novel PRO instrument for use in lower extremity trauma patients.

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KEYWORDS

amputation; limb salvage; lower extremity; trauma; survey; questionnaire; patient reported outcome measures; quality of life; patient satisfaction

Introduction

Background

Each year there are thousands of civilian and military limb-threatening lower extremity traumatic injuries [1,2]. Treatment for this is lengthy, with a time and resource burden both for patients and the health system. The outcomes include limb salvage, amputation, or delayed amputation after a failed attempt at reconstruction. It has not yet been established if attempted limb salvage or amputation results in better function, satisfaction, or quality of life for the patient [3,4]. To adequately answer these questions and other important research questions in the management of these patients, a well-defined, valid, reliable, and responsive patient-reported outcome (PRO) instrument is needed. PRO instruments are rating scales that measure concepts of interest (COI) relevant to patients such as the symptoms, appearance, function, and quality of life by asking the patients directly, without interpretation by a clinician or researcher [5].

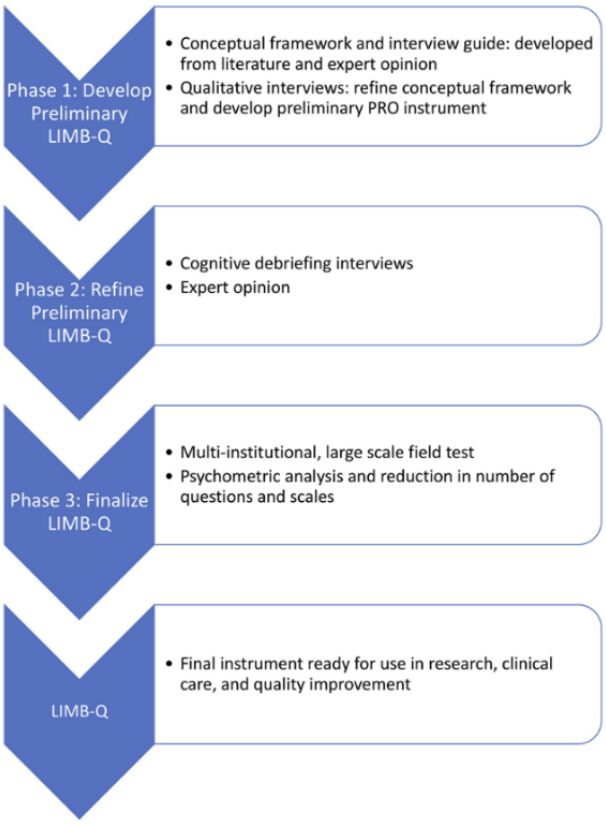
Numerous PRO instruments have been used in the past to study this patient population, such as the Sickness Impact Profile [6,7] and the Short Musculoskeletal Function Assessment Questionnaire [8]; however, all were developed either for the general population or specific to alternate diseases [9,10]. Despite the previous use of these instruments in lower extremity trauma patients, none were developed specifically for this cohort and, as a result, they lack content specific to this patient population. Therefore, although previous research has been rigorous and well-designed to identify differences in outcomes between the treatment cohorts, the interpretation of these results is limited by inadequate outcome measures used, as they were not designed to address the particular concerns of lower extremity trauma patients.

Objectives

To ensure that all important COI of these patients are measured and to answer important clinical questions regarding limb reconstruction and amputation, a well-defined PRO instrument designed specifically for lower extremity trauma patients is needed. This instrument should cover common and unique concerns of amputees and limb-reconstruction patients.

The following protocol is the result of an international collaboration whose primary focus is the development and validation of a new PRO instrument, developed specifically for patients after lower extremity trauma, to measure all important COI from the patient's perspective, applicable to both amputation and reconstruction patients; see Figure 1.

Figure 1. Phases of instrument development. PRO: patient-reported outcome.



Methods

Overview

The aim of this study is to develop a PRO instrument, with a set of independently functioning scales, that captures the multidimensional impact of lower extremity traumatic injuries on patients, useful for clinical practice, quality improvement, and research. Our team follows rigorous, state-of-the-art psychometric methodology for PRO instrument development [5,11-19], utilizing a multiphase mixed-methods approach [20]. Our approach involves 3 main phases of instrument development, which are completed in an iterative and interactive

manner. Briefly, the first phase identifies what the instrument should measure through the development of a preliminary conceptual framework from a literature review, followed by qualitative interviews, which are utilized to finalize the conceptual framework and develop the preliminary set of scales. The second phase refines the PRO instrument via cognitive debriefing interviews and solicitation of expert opinion. Finally, the third phase involves a large-scale field test and psychometric evaluation and refinement of items and scales. Adherence to the international guidelines for PRO instrument development ensures that the PRO instrument is scientifically sound (reliable, valid, and responsive). The first 2 phases of instrument development are presented here.

Conceptual Framework

The conceptual framework describes the COI within the patient group, helping to organize and frame the domains that are of importance to patients, and therefore should be under consideration for inclusion in the PRO instrument [5]. The preliminary conceptual framework was developed from the COI identified in our systematic review of the literature, in addition to expert opinion; see Textbox 1 [9]. The preliminary conceptual framework is then further refined through the qualitative portion of the study. The final conceptual framework maps all COI identified through the qualitative interviews and is used to define the domains within the preliminary set of scales.

Textbox 1. Preliminary conceptual framework domains.

- Appearance
- Employment
- Physical function
- Prostheses and orthotics
- Psychosocial well-being
- Satisfaction with experience
- Satisfaction with outcome
- Sexual well-being

Qualitative Study

This is a qualitative study designed to identify the concepts that are most important to lower extremity trauma patients via semistructured qualitative interviews. An interpretive description approach is utilized, with theoretical knowledge from the systematic review and clinical knowledge from the clinical team members, forming a basis for the identification of the COI for this patient group [21].

Participants

Inclusion criteria include patients aged 18 years or above, who suffered a lower extremity traumatic injury, distal to the midfemur, resulting in the need for reconstruction or amputation. Patients who do not speak English are excluded. A member of the clinical team recruits patients either face-to-face in the hospital or clinic or over the telephone. Interested participants who are unable to travel to the interview are offered phone interviews.

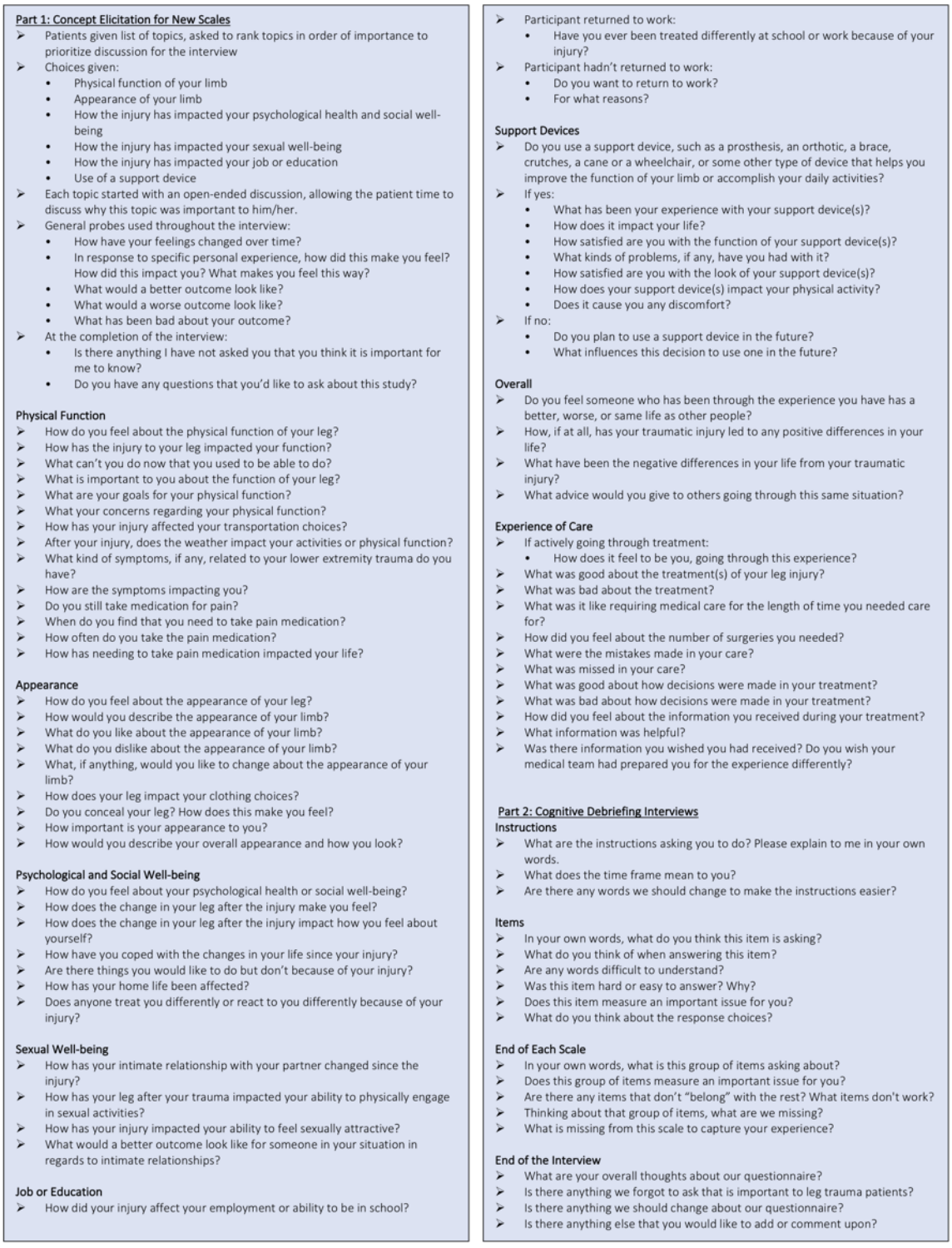
Sampling

Purposeful sampling maximizes participant variability to ensure a diverse group of participants, reflected in demographic variables (age, gender, and race), injury etiology, time since injury, and injury outcome (reconstruction, amputation, or amputation after failed reconstruction). Patients having undergone successful limb salvage, early amputation, and late amputation after failed attempts at reconstruction with varying amounts of time from initial injury will be recruited. Recruitment continues until content saturation is reached, that is, no new concepts are being identified in the interviews [22].

Data Collection

Consent is provided before participation. Demographic characteristics include age, gender, and race and clinical characteristics include medical history, drug/tobacco use, injury etiology, injury characteristics, date of injury, and surgical history, in addition to postinjury findings such as return-to-work status and chronic pain medication use. Trained qualitative researchers perform interviews using an interview guide developed to reflect the preliminary conceptual framework to ensure that all previously identified COI are addressed. The interview guide is a working document that is updated throughout the study as new COI are identified; see Figure 2.

Figure 2. Qualitative interview guide.



Part 1: Concept Elicitation for New Scales

- Patients given list of topics, asked to rank topics in order of importance to prioritize discussion for the interview
- Choices given:
  - Physical function of your limb
  - Appearance of your limb
  - How the injury has impacted your psychological health and social well-being
  - How the injury has impacted your sexual well-being
  - How the injury has impacted your job or education
  - Use of a support device
- Each topic started with an open-ended discussion, allowing the patient time to discuss why this topic was important to him/her.
- General probes used throughout the interview:
  - How have your feelings changed over time?
  - In response to specific personal experience, how did this make you feel? How did this impact you? What makes you feel this way?
  - What would a better outcome look like?
  - What would a worse outcome look like?
  - What has been bad about your outcome?
- At the completion of the interview:
  - Is there anything I have not asked you that you think it is important for me to know?
  - Do you have any questions that you'd like to ask about this study?

Physical Function

- How do you feel about the physical function of your leg?
- How has the injury to your leg impacted your function?
- What can't you do now that you used to be able to do?
- What is important to you about the function of your leg?
- What are your goals for your physical function?
- What your concerns regarding your physical function?
- How has your injury affected your transportation choices?
- After your injury, does the weather impact your activities or physical function?
- What kind of symptoms, if any, related to your lower extremity trauma do you have?
- How are the symptoms impacting you?
- Do you still take medication for pain?
- When do you find that you need to take pain medication?
- How often do you take the pain medication?
- How has needing to take pain medication impacted your life?

Appearance

- How do you feel about the appearance of your leg?
- How would you describe the appearance of your limb?
- What do you like about the appearance of your limb?
- What do you dislike about the appearance of your limb?
- What, if anything, would you like to change about the appearance of your limb?
- How does your leg impact your clothing choices?
- Do you conceal your leg? How does this make you feel?
- How important is your appearance to you?
- How would you describe your overall appearance and how you look?

Psychological and Social Well-being

- How do you feel about your psychological health or social well-being?
- How does the change in your leg after the injury make you feel?
- How does the change in your leg after the injury impact how you feel about yourself?
- How have you coped with the changes in your life since your injury?
- Are there things you would like to do but don't because of your injury?
- How has your home life been affected?
- Does anyone treat you differently or react to you differently because of your injury?

Sexual Well-being

- How has your intimate relationship with your partner changed since the injury?
- How has your leg after your trauma impacted your ability to physically engage in sexual activities?
- How has your injury impacted your ability to feel sexually attractive?
- What would a better outcome look like for someone in your situation in regards to intimate relationships?

Job or Education

- How did your injury affect your employment or ability to be in school?
- Participant returned to work:
  - Have you ever been treated differently at school or work because of your injury?
- Participant hadn't returned to work:
  - Do you want to return to work?
  - For what reasons?

Support Devices

- Do you use a support device, such as a prosthesis, an orthotic, a brace, crutches, a cane or a wheelchair, or some other type of device that helps you improve the function of your limb or accomplish your daily activities?
- If yes:
  - What has been your experience with your support device(s)?
  - How does it impact your life?
  - How satisfied are you with the function of your support device(s)?
  - What kinds of problems, if any, have you had with it?
  - How satisfied are you with the look of your support device(s)?
  - How does your support device(s) impact your physical activity?
  - Does it cause you any discomfort?
- If no:
  - Do you plan to use a support device in the future?
  - What influences this decision to use one in the future?

Overall

- Do you feel someone who has been through the experience you have has a better, worse, or same life as other people?
- How, if at all, has your traumatic injury led to any positive differences in your life?
- What have been the negative differences in your life from your traumatic injury?
- What advice would you give to others going through this same situation?

Experience of Care

- If actively going through treatment:
  - How does it feel to be you, going through this experience?
- What was good about the treatment(s) of your leg injury?
- What was bad about the treatment?
- What was it like requiring medical care for the length of time you needed care for?
- How did you feel about the number of surgeries you needed?
- What were the mistakes made in your care?
- What was missed in your care?
- What was good about how decisions were made in your treatment?
- What was bad about how decisions were made in your treatment?
- How did you feel about the information you received during your treatment?
- What information was helpful?
- Was there information you wished you had received? Do you wish your medical team had prepared you for the experience differently?

Part 2: Cognitive Debriefing Interviews

Instructions

- What are the instructions asking you to do? Please explain to me in your own words.
- What does the time frame mean to you?
- Are there any words we should change to make the instructions easier?

Items

- In your own words, what do you think this item is asking?
- What do you think of when answering this item?
- Are any words difficult to understand?
- Was this item hard or easy to answer? Why?
- Does this item measure an important issue for you?
- What do you think about the response choices?

End of Each Scale

- In your own words, what is this group of items asking about?
- Does this group of items measure an important issue for you?
- Are there any items that don't "belong" with the rest? What items don't work?
- Thinking about that group of items, what are we missing?
- What is missing from this scale to capture your experience?

End of the Interview

- What are your overall thoughts about our questionnaire?
- Is there anything we forgot to ask that is important to leg trauma patients?
- Is there anything we should change about our questionnaire?
- Is there anything else that you would like to add or comment upon?

Data Analysis

Interviews are recorded and transcribed verbatim. Each interview is coded line by line to identify COI, categorized top-down into domains, followed by themes and subthemes. Interviews are coded as a team by a clinical expert (LRM) and qualitative methods expert (AK) to ensure consistency, reliability, and validity in coding. Coding questions requiring additional clinical expertise were discussed with additional clinical experts (MJG and STH) as needed. Constant comparison is used to ensure consistency in coding, allowing for continuous refinement of previously coded data [23]. It must be noted that more than 1 item can be generated from a code if the participant uses different words/phrases to describe their thoughts or experiences. However, if someone uses the same word/phrase repeatedly, we develop 1 item for the concept as we are interested in capturing a unique concept rather than capturing the number of times a subject repeats himself or herself. The

domains are used to generate the final conceptual framework, organizing all identified COI.

Item Generation

The codes generated in the data analysis process represent an exhaustive list of all relevant COI to lower extremity trauma patients, organized through the lens of the conceptual framework. Each domain within the conceptual framework that is relevant to clinical care or research is utilized to develop a preliminary scale. Coded text with major/minor themes is moved into an Excel spreadsheet (Microsoft Excel 2016) along with the participant's age, gender, and surgical outcome (reconstruction, amputation, or reconstruction to amputation). Clinical data are utilized to identify the codes that are relevant across patient groups versus the codes that are relevant to only a specific patient group, such as concerns specific to patients with prostheses. Each code is examined in turn to generate a preliminary item pool for scale development. Within each scale, the items are developed from the themes and subthemes, using as many of the participants' own words as possible. For each scale, instructions and response options are added. Our goal is to keep the scales simple and in line with the published guidelines [24]. Khadka et al demonstrated that rating scales or questionnaires with a complicated question format, with a large number of response categories or with unlabeled categories tended to be dysfunctional and recommended that PRO instruments should have simple question formats and only a few (4-5 at most) response options and that all response options should be labeled [24].

Refining the Preliminary Scales

The preliminary PRO instrument scales are refined via patient interviews and solicitation of expert opinion in phase II of instrument development, ensuring maximum content clarity and comprehensiveness [19].

Cognitive Debriefing Interviews

Semistructured interviews are conducted with lower extremity trauma patients to assess for content and clarity of wording, ensuring the instrument is comprehensive, relevant, and comprehensible. Participants meeting the same inclusion/exclusion criteria stated previously are recruited in a similar manner. Recruitment starts with the initial qualitative interview of participants and then, if needed, is expanded to additional patients meeting the above inclusion criteria, who did not participate in the first round of interviews. Participants are interviewed one-on-one by a trained qualitative interviewer, with the participant going through the scale line by line using the think-aloud technique, explaining out loud how the participant interprets each item [25]. Participants are also asked to comment on the instructions, probed for missing content, and asked to identify problematic items and scales. Consequently, the instrument is prepared for the large-scale field test, combining revisions from the opinions of expert clinicians.

Expert Clinical Input

In concurrence with soliciting opinions from patients, the opinions of expert clinicians are solicited. This is to ensure that the PRO instrument captures all key concepts relevant to clinicians or researchers. Expert advice is sought from clinicians, including plastic and orthopedic surgeons, in addition to the physical and occupational therapists, nursing, prosthetists, and limb-loss experts. Experts provide written feedback on the instrument via a written survey.

Results

Phases I and II of this study have been funded. Phase I of this study has been completed, and phase II began in January 2019 and is expected to be completed in November 2019. Phase III will begin following the completion of phase II.

Next Steps

Pilot Field Test

A pilot field test is carried out before the large-scale international field test. The goal of the pilot field test is 2-fold: first, to identify and address any administrative or logistical difficulties, and second, to perform a preliminary Rasch analysis to identify and address any psychometric issues with LIMB-Q scale performance. Inclusion criteria are similar to those described above. Participants complete the LIMB-Q in addition to providing demographic, injury, and treatment information. Rasch measurement theory (RMT) is used to drive the data analysis of the scales and is described in detail in the following section.

International Field Test

A large-scale international field test is the final stage in LIMB-Q development, with the goal to finalize the items and scales of the LIMB-Q, determining scale validity, reliability, and responsiveness. Inclusion criteria are similar to what is described above, with participants recruited from multiple centers in different countries. Centers are selected based on the interest and feasibility of recruitment. In addition to completing the LIMB-Q, participants provide demographic, injury, and treatment information. A small subset of participants complete the LIMB-Q at 2 points, 1 to 2 weeks apart, to allow for an assessment of test-retest reliability. Each scale is analyzed independently so that it may stand alone.

Rasch Measurement Theory

In the RMT, the focus is on the relationship between a person's measurement and his or her probability of responding to an item in a scale [13]. The RMT places individuals onto a *ruler* based on the likelihood of giving a certain answer [26]. The qualitative phase of instrument development allows for the creation sample to fit on the *ruler*, with room to move up or down with treatment, making for scientifically sound and clinically meaningful scales. The RMT analysis identifies the subset of items that are the best indicators of a scale's concept based on the performance and set of psychometric tests and criteria. Briefly, the psychometric testing of the instrument following the field test will involve several steps. The first will be to assess the psychometric functioning of the items and scales. The thresholds for item response options will be ordered into a hierarchy of items on the scale from the easiest to the most difficult questions. Next, 3 item-fit statistical tests will be employed to determine if the items work well together within a set. These include log residual for item-person interaction, chi-square values for item-trait

interaction, and item characteristic curves. Outside of the clinically important items, items not meeting all 3 characteristics will be dropped from the scale. Finally, construct validity is confirmed by comparing the range of the construct measured by the scale with the range experienced by the population. Following these initial steps, the internal consistency, that is, the interrelatedness of items on a scale, will be confirmed with testing for unidimensionality and evaluating the Person Separation Index. In addition, differential item functioning will be evaluated, and items will be reduced accordingly. Items will be reduced that either represent redundancy or overlap on the ruler or are poorly functioning. The steps outlined above will result in a final version of the LIMB-Q and associated scoring table for each scale. Following the development of the finalized scales, construct validity, reliability with internal consistency and test-retest reliability, validity with content, construct and criterion validity, and responsiveness to change will be established.

Discussion

Principal Findings

This study is the first to our knowledge to develop a PRO instrument specific to lower extremity trauma patients, applicable to both amputees and limb-salvage patients. A major limitation in previous lower extremity trauma research has been the lack of an appropriate outcome measure that is capable of assessing all COI relevant to both limb-reconstruction patients and amputees [9,10].

The outcome measures currently used to evaluate these patients include functional scales and generic or disease-specific PRO instruments not developed specifically for the lower extremity trauma population. The Lower Extremity Functional Scale [27] or the Locomotor Capabilities Index [28] are functional instruments that provide data deemed important to clinicians and researchers. To evaluate the patient's perspective, generic PRO instruments, such as the Sickness Impact Profile [6,7] and 36-Item Short Form Health Survey questionnaire [29], or generic musculoskeletal instruments, such as the American Orthopedic Foot and Ankle Score Ankle-Hindfoot and Midfoot Rating Scales [30] and Short Musculoskeletal Function Assessment Questionnaire [8], along with disease-specific instruments not developed for but applied to lower extremity trauma patients, such as the Musculoskeletal Tumor Society [31] and Toronto Extremity Salvage Score [32], are frequently used. Although these instruments are reliable and valid for the general population, or for their respective musculoskeletal disease cohort, they lack the detail needed to measure clinical change in a reliable or meaningful way for these trauma patients [33]. PRO instruments focusing on patients who have undergone only amputation are in use [34]; however, there is no PRO instrument that is designed for all patients with limb-threatening lower extremity traumatic injuries that measures COI relevant to both reconstruction and amputation patient groups.

Strengths and Limitations

The goal of this protocol is to compete phases I and II of the development of a PRO instrument for lower extremity trauma patients. In future stages, our multidisciplinary team will utilize RMT to finalize the development and validation of LIMB-Q, comprising a comprehensive set of clinically meaningful scales, measuring COI important to patients with limb-threatening lower extremity injuries. The scales will be designed for use in research and direct clinical care, applicable to patients who undergo either limb salvage or amputation. The inclusion of patients at varying time points from injury in the development of this instrument will provide for an agile instrument capable of providing meaningful information to clinicians and patients over the duration of a patient's treatment course. This instrument will have the capability to measure incremental differences in outcomes important to patients and allow for direct comparison between treatment modalities for severe lower extremity trauma. Clinically, this tool will provide patients with a structured and reliable method for communicating outcomes to providers and will provide accurate and objective feedback to improve clinical care.

Conclusions

The LIMB-Q will be a novel PRO instrument for use in lower extremity trauma patients, available for use in research and clinical care. Rigorously developed and validated, the LIMB-Q will have the capability to measure COI relevant to lower extremity trauma patients, to help us better care for and understand the needs of these patients with challenging and often devastating injuries.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 579 KB - resprot_v8i10e14397_app1.pdf]

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Abbreviations

COI: concepts of interest
PRO: patient-reported outcome
RMT: Rasch measurement theory

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Protocol

A Salutogenic Approach to Understanding the Potential of Green Programs for the Rehabilitation of Young Employees With Burnout: Protocol for a Mixed Method Study on Effectiveness and Effective Elements

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Abstract

Background: Burnout is the leading cause of absenteeism in the Netherlands, with associated sick leave costs amounting to around €1.8 billion. Studies have indicated that burnout complaints increased from almost 14.4% in 2014 to 17.3% in 2018, especially among employees between the ages of 18 and 35 years, and further increases are expected. Although there are many published articles on burnout, not much is known about what constitutes effective rehabilitation (ie, the reduction of burnout complaints and the facilitation of returning to work). At the same time, multiple pilot studies have indicated that green programs are effective in both reducing burnout complaints and facilitating return to work. Green programs have been developed by professionals experienced in using the natural environment to facilitate rehabilitation (eg, through green exercise and healing gardens). The literature nevertheless lacks comprehensive and contextual insight into what works and why.

Objective: The overarching aim of this study is to explore the potential of green programs for young employees with burnout. We present the study protocol from an ongoing research project consisting of 2 phases, each composed of 2 research objectives that sequentially build upon each other.

Methods: The study is based on a sequential design with 4 research objectives, using both qualitative and quantitative research methods. In the first phase, a systematic literature review (research objective 1) and in-depth interviews (research objective 2) will be used to explore mechanisms underlying the rehabilitation of young employees with burnout. In the second phase, a multicase study will be conducted to examine the extent to which green programs are built on mechanisms identified in the first phase (research objective 3). By employing a pretest and posttest design, a specific green program that captures most of those mechanisms will then be evaluated on its effect and process with regard to the rehabilitation of young employees with burnout (research objective 4). The project started in June 2018 and will continue through June 2022.

Results: The first phase (research objectives 1 and 2) is intended to generate information on the mechanisms underlying the rehabilitation of young employees with burnout. The second phase (research objectives 3 and 4) is designed to demonstrate the extent to which and how the selected green program facilitates the rehabilitation of young employees with burnout.

Conclusions: Understanding how green programs can facilitate the rehabilitation of young employees with burnout complaints can help to address this societal issue.

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KEYWORDS

burnout; health promotion; occupational health; program evaluation; rehabilitation; sense of coherence; workforce

Introduction

Background

Work-related stress is the leading cause of absenteeism in the Organization for Economic Cooperation and Development countries [1,2], and it is accompanied by significant financial consequences for society [3]. The most significant occupational syndrome, burnout, has been shown to have an adverse effect on the health and well-being of employees (eg, more physical illness) and on the organizations in which they work (eg, less organizational involvement) [4]. In the Netherlands, burnout is the leading cause of absenteeism, with associated sick leave costs amounting to around €1.8 billion [5]. The prevalence of employees with burnout complaints has increased from 14.4% in 2014 to 17.3% in 2018 [6], especially among employees between the ages of 18 and 35 years [7]. Given that organizational development and performance are dependent on the health and well-being of employees [8], it is of utmost importance to address the increase of burnout among young employees.

Burnout is defined as "a work-related state of exhaustion that occurs among employees, which is characterized by extreme tiredness, reduced ability to regulate cognitive and emotional processes, and mental distancing. These four core dimensions of burnout are accompanied by depressed mood as well as by non-specific psychological and psychosomatic distress symptoms" [9]. In general, the development of burnout is fostered through a complex interplay of factors within employees (eg, being a workaholic), factors within the organizational context (eg, excessive workload) [10], and factors beyond the workplace (eg, economic crisis) [11]. Little has been written, however, about the recent increase in burnout complaints among young employees.

The early 1970s witnessed the emergence of a booming burnout industry, consisting of programs focusing on either employees (ie, person-directed interventions) or organizations (ie, organization-directed interventions) [4,12,13]. A further distinction can be made between programs aimed at reducing burnout complaints among employees who are still at work and interventions aimed at facilitating return to work (RTW) among employees who are currently not working because of burnout [4]. Systematic reviews and meta-analyses have focused on either person-directed or organization-directed interventions, indicating that the use of either of these types of interventions alone produces suboptimal results in terms of reducing burnout complaints and facilitating full RTW [14,15]. Burnout programs that combine both person-directed and organization-directed interventions are more likely to be effective in facilitating rehabilitation. Reviews of such programs are nevertheless lacking.

At the same time, a growing body of literature suggests that nature offers opportunities for rehabilitation [16], here defined as developing the ability of young employees to participate and be productive in a sustainable and meaningful way [17]. Studies have demonstrated that experiencing nature can directly enhance physical and mental health and that interacting with natural elements can develop well-being, while offering opportunities for social interaction [18]. These empirical insights are increasingly being translated into "green programs" aimed at facilitating the rehabilitation of employees with burnout [19]. Little is known, however, about the extent to which green programs can facilitate rehabilitation for young employees with burnout.

Typical examples of green programs include green exercise [20] and healing gardens [21]. These programs differ in the *extent* to which nature is used, as well as in the *ways* in which nature is used [22]. One defining characteristic of green programs is that they are provided by professionals who are experienced in using nature to facilitate rehabilitation. Although the first pilot studies indicate that green programs can reduce burnout complaints and facilitate RTW [19,20], not much is known about their effectiveness or underlying mechanisms. The aim of this study is, therefore, to explore the potential of green programs for the rehabilitation of young employees (18-35 years of age) with burnout in the Netherlands.

Research Objectives

We present the study protocol from an ongoing research project consisting of 2 phases, each proceeding from 2 research objectives that build sequentially upon each other. Before we can understand how green programs could facilitate rehabilitation among young employees with burnout, we must understand the mechanisms underlying such rehabilitation (phase 1). The next logical step is to examine the extent to which green programs are built on those mechanisms and to evaluate a green program on its effect and process for young employees with burnout (phase 2). In line with the overall research objective, the emphasis of this study lies in phase 2. Given the limited knowledge about the rehabilitation of young employees with burnout, however, phase 1 is of utmost importance to the research project.

Phase 1

Research Objective 1

Systematic reviews and meta-analyses have focused on either person-directed or organization-directed interventions, each of which has proved suboptimal in promoting rehabilitation when used exclusively. The first objective of this study is, therefore, to assess the effectiveness of existing combined rehabilitation programs, in addition to examining the mechanisms that influence their effectiveness.

Research Objective 2

The increase in burnout complaints among young employees is a recent phenomenon. It is, therefore, necessary to understand how young employees develop and recover from burnout. To this end, the second objective is to understand factors relating to the development of burnout and rehabilitation from burnout among young employees.

Phase 2

Research Objective 3

Although green programs are increasingly assumed to be effective in the rehabilitation of employees with burnout, the extent to which their initiators have built upon the mechanisms identified in phase 1 is unclear. The third objective is, therefore, to describe green programs and examine the extent to which they are built on mechanisms underlying the successful rehabilitation of young employees with burnout.

Research Objective 4

To date, there is little understanding concerning the relative effectiveness of green programs in the rehabilitation of young employees with burnout and with regard to the reasons underlying their effectiveness. To address this knowledge gap, the fourth objective of this study is to evaluate the effect and process of a green program for young employees with burnout. The rationale for evaluating only 1 green program is that doing so can ensure the feasibility of the study, with a specific focus on a program that captures most of the mechanisms identified in the first phase.

Theoretical Framework

This study integrates theories that explain associations between nature and rehabilitation, in addition to drawing on pivotal theories used in health promotion.

Nature and Rehabilitation

Associations between nature and rehabilitation are assumed to be explained by 4 types of pathways: physiological, mental recovery, social, and psychological [16,18]. The physiological pathway refers to the beneficial effects that being outside and physically active can have on physical well-being or other aspects [18]. The mental recovery pathway alludes to the effects that the “soft fascination” of being in nature can have on acute and chronic stress (eg, improved mood) [18]. The social pathway elicits the positive effects of social contacts that nature may facilitate (eg, a sense of belonging) [18]. The psychological pathway touches on the capacity of nature to serve as a mirror with which to reflect on concrete experiences (eg, through the use of metaphors). These 4 pathways are intertwined. For example, acute or chronic stress can be alleviated by physical activity in the same way that having social contacts can influence reflection [16].

The Salutogenic Approach

This study adopts the salutogenic approach to investigate how the 4 pathways underlying green programs can facilitate rehabilitation. The salutogenic approach focuses on the processes through which young employees can strengthen (or restore) their capacity to identify and reuse resources within themselves (eg, skills), as well as within their immediate environments (eg, social relations) to deal with stressors (eg, daily hassles) [23]. In this regard, it complements pathogenic strategies aimed at eliminating or alleviating stressors in the workplace. Studies have demonstrated that enhancing resources and people’s capacity to use and reuse those resources can have more sustainable effects as compared with efforts aimed at eliminating stressors [23]. The salutogenic processes underlying this capacity depend primarily on environmental support for certain experiences [23]. The 4 pathways are likely to provide this support. For example, feeling physically and mentally well (ie, the physiological and mental recovery pathways) are inherent resources that enable young employees to deal with stressors. For this reason, this study adopts the salutogenic approach as an overarching framework with which to examine how green programs can support the salutogenic process, thereby facilitating rehabilitation for young employees with burnout.

The resources that can be used to deal with stressors effectively are known as *generalized resistance resources* (GRRs) [24]. The ability to use (or reuse) GRRs is known as the *sense of coherence* (SOC), a global life orientation that represents the extent to which people experience the world as comprehensible, manageable, and meaningful [25]. Studies have indicated that GRRs maintain a reciprocal relationship with SOC. In other words, GRRs predict a high SOC, which in turn enhances the ability to identify and use GRRs [26]. Important GRRs in the workplace include job control, social relations, and task significance [27]. Job control is defined as an employee’s decision-making authority, opportunities to use skills and knowledge, and opportunities to participate [17]. Social relations are defined as the extent to which individuals are able to count on information, assistance, support, and appreciation from their colleagues at work [17]. Task significance is defined as the perception that an individual’s job has a positive impact on other people [17]. Although resources are not GRRs unless an employee can use them [23], this study uses these 3 GRRs and SOC as indicators of rehabilitation among young employees.

Research has consistently demonstrated that employees with a strong SOC experience fewer burnout complaints than do employees with a weak SOC [28]. Understanding the salutogenic process through which the 4 pathways can strengthen the SOC of young employees could, therefore, enhance insight into how green programs can facilitate their rehabilitation. However, little is known about this salutogenic process. It can nevertheless be explained by attribution theory [29], which is intended to explain how and in what way people process information in the attempt to understand events, judge those events, and act on those events [30]. Attribution theory is strongly related to the 3 dimensions of SOC—comprehensibility (understanding events), manageability (acting on events), and meaningfulness (judging events) [30,31]—thus making it possible to study the development of SOC.

Taken together, the aforementioned theories offer a coherent framework with which to explain how green programs can facilitate the rehabilitation of young employees with burnout (see Figure 1). As shown in the figure, the 4 pathways are likely to provide environmental support for certain experiences that can enhance the GRRs and SOC of young employees. For example, feelings of mental and physical well-being are inherently GRRs (mental recovery and physiological pathways), as is having social relations (social pathway). In addition, the psychological pathway can foster an employee’s reflection on positive life experiences, with nature serving as a mirror. By reflecting on such experiences, young employees can shed light on exactly what has happened in terms of stressors and the GRRs at their disposal (comprehensibility), in addition to

understanding how they have taken action to use their GRRs (manageability) and making sense of why dealing with those stressors was worthwhile (meaningfulness). This salutogenic process is assumed to enhance both the GRRs and the SOC of young employees, thereby facilitating their rehabilitation.

Figure 1. Conceptual framework. SOC: sense of coherence; GRR: generalized resistance resource; RTW: return to work.

Methods

Study Design

This study is based on a sequential exploratory research design involving mixed method—more specifically, a combination of qualitative and quantitative research methods [32]. In the following sections, the research methods and activities are explained for each research objective.

Methods and Activities for Phase 1

The first phase is intended to identify mechanisms underlying the rehabilitation of young employees with burnout. First, a systematic review will be conducted to assess the effectiveness of existing combined rehabilitation programs as well as factors underlying their effectiveness (research objective 1). Second, interviews with young employees will be used to investigate factors related to the development of burnout and rehabilitation (research objective 2).

Research Objective 1

Method

A systematic review will be employed according to the guidelines for Reporting Items for Systematic Reviews and Meta-Analyses [33]. Details of the protocol for this systematic review have been registered on PROSPERO [34].

Activities

A total of 7 electronic databases are searched: Psychology and Behavioral Sciences Collection, PsycARTICLES, Web of Science (all databases), Scopus, SocINDEX, PubMed, and PsycINFO. Search terms are based on the operationalization of burnout according to the most frequently used questionnaire for measuring burnout—the Maslach Burnout Inventory (MBI)—combined with *intervention*. The inclusion period will be specified from 1970 to 2019. No other electronic search strategies will be employed, as the literature review will not include gray literature and non–peer reviewed publications. The reference lists of the articles reviewed and the systematic reviews identified will also be searched for additional relevant studies.

A total of 5 inclusion and exclusion criteria will be applied to the studies identified through the search. First, only interventions that combined both person-directed and organization-directed approaches (eg, cognitive-based therapy with interventions in the workplace) will be included. Second, studies that do not use the MBI to measure burnout will be excluded. Third, only experimental study designs will be included (eg, cross-sectional studies will be excluded). Fourth, only studies focusing on employees will be included. Finally, only studies reported in English will be included.

We will use a descriptive narrative synthesis of the effects of the programs on burnout or RTW that are included using summary data published in the articles. In addition, a detailed description of each study will be compiled, including participant characteristics, the theory and approach used, levels targeted, program content, and the duration and intensity of the program. All researchers will be involved in synthesizing the data and the resolution of any discrepancies.

Research Objective 2

Method

A total of 20 open semistructured interviews will be conducted with young employees who have either been diagnosed with burnout or have successfully recovered from a diagnosed burnout. If needed, additional interviews will be conducted until data saturation is achieved. For the purposes of this study, successful recovery will be defined as full RTW, whether with the employee's current employer or with a new employer. A narrative inquiry approach will be used to investigate the mechanisms underlying the development of burnout in young employees and how their rehabilitation proceeded. Narrative inquiry is defined as systematically listening to people's life stories [35]. These stories will be elicited through timelines—an established research tool involving drawing and visually exploring life experiences [36]. The drawings and visually explored life experiences will then be used to structure the open semistructured interviews. For example, participants will discuss and explain their timelines chronologically and describe life events and turning points with regard to the development of burnout and subsequent rehabilitation.

Activities

We will recruit young employees (18-35 years of age) who have either been diagnosed with burnout or have successfully recovered from a diagnosed burnout. As a criterion for inclusion, an employee's diagnosis must have been made by an occupational physician or general practitioner. As a criterion for exclusion, the burnout must not have been a direct consequence of a psychiatric disorder (eg, clinical depression), which can be ascertained according to the official process for diagnosing burnout in the Netherlands [37]. Participants will be recruited through social media (eg, Twitter and Facebook) and the distribution of flyers about the study in the offices of occupational physicians and general practitioners, thereby enabling employees to contact the researchers directly for additional information concerning participation in the study.

Atlas.ti 8 (Windows) software will be used to analyze the data. All researchers will code the transcriptions of the qualitative data. Interview transcripts will be analyzed using interpretative phenomenological analysis, which takes the world of participants into account and analyzes the articulation of events, processes, and relationships [38]. Any lack of congruence will be discussed until an agreement is reached. Particular attention will be given to (1) stressors, (2) attributions, (3) GRRs, and (4) SOC.

Methods and Activities for Phase 2

The second phase is intended to examine the extent to which green programs are built on mechanisms identified in the first phase (research objective 3) and to evaluate a green program on its effect and process for young employees with burnout (research objective 4).

Research Objective 3

Method

A multiple case study will be used [39] to pursue this objective. Focus group interviews with the initiators of green programs will be used to collect data contributing to the description of the green programs, complemented by individual open semistructured interviews with initiators.

Activities

An inventory of green programs available in the Netherlands will be compiled in collaboration with several stakeholders involved in this project. As criteria for inclusion, a green program must target young employees with burnout and have been developed by practitioners with ample experience using nature to facilitate rehabilitation.

Using a purposive sampling strategy, a heterogeneous sample of a maximum of 10 green programs will be selected. Focus group interviews with the initiators of green programs will be used to describe the programs, focusing on the following characteristics: underlying theoretical assumptions, methodologies used, program aims and content, processes, outcome measures, and follow-up. This information will be complemented by individual open semistructured interviews with each of the same initiators.

Atlas.ti 8 (Windows) software will be used to analyze the data. The transcriptions of qualitative data will be coded by all researchers, informed by the mechanisms underlying rehabilitation, as identified in research objectives 1 and 2. First, a within-case analysis [38] will be conducted to obtain a thorough description of the development of the selected green programs. Second, a cross-case analysis [39] will be conducted to develop a comprehensive description of green programs and the extent to which they are built on the mechanisms underlying the rehabilitation of young employees with burnout, as identified in research objectives 1 and 2.

Research Objective 4

Method

A pretest and posttest design will be used to conduct an effect and process evaluation of an existing green program aimed at the rehabilitation of young employees with burnout [29]. A pretest (T0) measurement will be taken at the start of the green program, with the posttest (T1) measurement being taken after the program has ended. This information will be supplemented with an additional follow-up (T2) measurement. The emphasis of this study is on understanding the extent to which the green program to be selected is effective in promoting the rehabilitation of young employees, in addition to considering how and why the program did or did not work. The next logical step would be to compare the effect and process of this program with those of another rehabilitation program, but doing so would be beyond the scope of this study.

Although the selection of the green program will depend on the mechanisms identified in phase 1 and on the expert advice provided by the advisory board (see section Discussion), the following 3 criteria have been predefined. First, the green

program should be officially registered with the Dutch Association for Green Care Professionals [40]. In other words, it should be conducted by a registered coach or therapist with specific expertise in using nature to facilitate rehabilitation. Second, the green program should take place outdoors. In other words, it should involve allowing the participants to experience nature (eg, walking outside while being coached) and to interact with its elements (eg, shaping nature). For example, placing plants in the offices of young employees would not be considered as a green program. Finally, the duration and frequency of the green program should be substantial. For example, a green program that offers a single walk outdoors would not be eligible.

The experimental and control groups will consist of young employees with either burnout complaints or a diagnosed burnout, who will then participate in the green program to be selected. The rationale for including young employees with burnout complaints, rather than only employees who are diagnosed with burnout, is to ensure that the number of participants included will be sufficient to measure the effects on their rehabilitation. Participants in the experimental group will participate in the green program to be selected, whereas the participants in the control will not be enrolled in a green program. However, it is likely that young employees in both groups will take action by themselves to cope with their burnout complaints or diagnosed burnout. Therefore, this study will examine those possible coping strategies in both groups (see the following section Activities) to better understand the effect and process of the green program.

To determine the number of participants in the experimental and control groups, formal sample size calculations will be employed using G*Power, version 3.0.10 based on 1 of the outcomes of rehabilitation: SOC, GRRs, RTW, or burnout complaints. The outcome used for the power calculation and the exact research design will be based on research objectives 1, 2, and 3.

Activities

Young employees who have been diagnosed with burnout (as explained in research objective 2) will be recruited through physicians/general practitioners, as these employees are not currently working because of burnout. The recruitment of young employees with burnout complaints who are currently still working will be done in a similar manner (eg, through social media and by placing flyers about the study in the offices of occupational physicians and general practitioners). In addition, employees will be approached through organizational newsletters, to recruit young employees with burnout complaints who do not use social media or contact their occupational physicians or general practitioners about their complaints.

The Burnout Assessment Tool (BAT) (33 items) is a reliable, validated Dutch questionnaire for measuring burnout complaints [9]. Although the MBI is the most frequently used questionnaire, it is subject to several conceptual, technical, and practical imperfections [9]. In contrast, the BAT is assumed to be more versatile, and it can even be used to assess and monitor employees who are currently not working (eg, within the context of RTW programs) [9]. Moreover, psychometric studies have demonstrated that the total score on the BAT can be used as an indicator of burnout [9].

The concept of SOC is easily applicable to workplaces. It will be measured using the Dutch version of the Orientation to Life Questionnaire (13 items) [41]. Given that SOC represents a global life orientation shaped by its 3 dimensions, the total SOC score will be calculated [40].

The Dutch versions of the Knowledge Intensive Working Environment Survey Target and the second version of the Copenhagen Psychosocial Questionnaire II have been validated to measure the 3 GRRs: job control (16 items), social relations (12 items), and task significance (3 items) [42,43]. Each of these questionnaires assesses a broad range of psychosocial work factors, and neither is attached to any specific theory or model. The various subscales will be combined into 3 latent variables [26,27].

The Causal Dimension Scale II (12 items) will be used to measure the attribution styles of young employees, operationalized according to 4 dimensions: locus of causality, stability, personal control, and external control [31]. As the questionnaire has not been validated in Dutch, it will be translated according to the cross-cultural adaption process [44].

RTW will be operationalized as the number of days until RTW or full RTW at follow-up.

The questionnaires selected for the effect evaluation are listed in Table 1. In addition to the instruments mentioned in the table, demographic information will be obtained through items concerning age, sex, country of birth, the highest level of education completed, and current (or previous) job. These data will be collected only at the T0 stage.

With regard to the effect evaluation, quantitative data will be assessed, particularly concerning the potential for bias because of nonresponse, the extent and pattern of missing data, and heterogeneity between groups [45]. The data will, therefore, be checked to determine whether nonresponse was related to gender, age, or other demographic variables, as well as whether any such associations could explain differences in response rates among the groups. The next step will involve assessing the psychometric properties of the data obtained by the instruments listed in Table 1 (eg, internal consistency, based on Cronbach alpha) and comparing them with the properties reported by their developers. The analyses will be performed using the IBM SPSS Statistics 24 software, based on descriptive statistics (eg, means, frequencies, and 1-way repeated-measures multivariate analysis of variance) [45].

Table 1. Questionnaires to be used for the effect evaluation.

Questionnaire	Captures	Domains	Likert scale
Burnout Assessment Tool [9]	Burnout complaints	• Exhaustion • Mental distance • Emotional impairment • Cognitive impairment • Depressed mood	1-5
Sense of coherence—Orientation to Life Questionnaire [41]	Comprehensibility, manageability, meaningfulness	• Manageability • Comprehensibility • Meaningfulness	1-7
Knowledge Intensive Working Environment Survey Target (KIWEST)/Copenhagen Psychosocial Questionnaire II (COPSOQ II) [42,43]	Job control (GRR[a])	• Influence on work • Possibilities for development • Job autonomy • Illegitimate tasks	1-5
KIWEST/COPSOQ II [42,43]	Social relations (GRR)	• Social support from supervisors • Social support from colleagues • Rewards • Social community at work	1-5
KIWEST/COPSOQ II [42,43]	Task significance (GRR)	• Meaning of work	1-5
Revised Causal Dimension Scale II [31]	Attribution style	• Locus of causality • Stability • Personal control • External control	1-9

[a]GRR: generalized resistance resource.

To better understand the extent to which the green program (to be selected) is effective in facilitating the rehabilitation of young employees with burnout, a process evaluation will be performed using open semistructured interviews with the study participants and initiators of green programs. The interviews will emphasize how the program has been executed, as well as mechanisms underlying how and why the program (see Figure 1) worked in relation to rehabilitation. Interviews will also be conducted with the study participants in the control group to explore how they have coped with their burnout complaints or diagnoses.

For the process evaluation, the open semistructured interviews will be recorded and transcribed verbatim. Atlas.ti 8 software will be used to explore the perceptions of the participants with regard to the program and pathways. Any lack of congruence will be discussed with all researchers until an agreement is reached. The rationale for the process evaluation is that it will provide comprehensive and contextual insight into what works and why. This insight will be further enhanced by examining how other possible coping strategies of young employees in both experimental and control groups could have contributed to their rehabilitation.

Results

The study protocol was reviewed and approved by the Research Assessment Committee from the Wageningen School of Social Sciences, Wageningen University and Research (Multimedia Appendix 1). The research project started in June 2018, and will continue through June 2022. This study protocol includes the methods and activities of 4 different studies that will build sequentially on each other. The first phase (research objectives 1 and 2) is intended to generate information on the mechanisms underlying the rehabilitation of young employees with burnout. The second phase (research objectives 3 and 4) is designed to demonstrate the extent to which and how the selected green program facilitates the rehabilitation of young employees with burnout. The first results are expected to be submitted for publication in 2020.

According to Dutch law, the research project requires formal ethical approval by the Social Sciences Ethics Committee (Wageningen University & Research). This approval was obtained on June 13, 2019. The activities associated with the fourth research objective require consent from the Medical Ethical Committee of Wageningen University, which will be requested during the third year of the project (2020/2021). It is not possible to apply for approval for this research objective at this stage of the project, as it builds on the information obtained through the other 3 research objectives. The required details of the experimental design for the fourth research objective are thus not yet available.

At every stage of the research, participants will be informed about the purpose and content of the study. Moreover, participation will always be voluntary, and participants will be able to withdraw from research activities for any reason at any time. Data confidentiality will be ensured by removing all personal information of the participants from the dataset.

Discussion

According to the Dutch Public Health Foresight Study, it is important to address burnout among young employees, as it is expected to increase further [46]. By examining mechanisms underlying the rehabilitation of young employees with burnout (phase 1) and examining whether and how green programs facilitate rehabilitation among young employees (phase 2), this study makes a direct contribution to addressing this societal problem.

Given that the BAT has not yet been used in evaluation research on burnout interventions, the systematic review (research objective 1) will be based on the MBI, as it continues to be regarded as the golden standard for measuring burnout. The effectiveness of the green program will be assessed according to the BAT, however, and this will also offer an opportunity to reflect on the validity and reliability of this instrument in intervention research.

A multicase, multi-method design is proposed, including several green programs, using both qualitative and quantitative measures. Rather than examining pathways underlying green programs in isolation, this study adopts a salutogenic approach to exploring the interrelatedness between pathways. This will make it possible to examine the salutogenic mechanisms through which green programs provide environmental support on certain experiences that strengthen young employees' GRRs and SOC, thereby enhancing insight into how to facilitate their rehabilitation.

Although the salutogenic approach takes the specific work contexts of employees into account, green programs often do not target their daily work environment. The authors acknowledge that improving the working conditions and working environments of young employees is also important to facilitate their rehabilitation. In addition, it would be good to have green programs that could combine their approach with workplace interventions. Given the emphasis of this research project on exploring the potential of green programs for the rehabilitation of young employees with burnout, however, the evaluation of workplace interventions would exceed the scope of this study.

Finally, to enhance the feasibility of this study, an advisory board has been established, consisting of experts from multiple institutions [47]. The overarching aim of the advisory board is to discuss the research project in terms of both content (eg, the research design for research objective 4) and process (eg, the recruitment of participants for research objective 2). Meetings will be organized at least twice a year, thereby allowing the researchers to anticipate and address problems that could threaten the feasibility of the project.

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Authors' Contributions

RP, LV, EV, and MK contributed to designing the study protocol. All authors are contributing to the implementation of the study. All authors commented on draft versions and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Wageningen School of Social Sciences.
[PDF File (Adobe PDF File), 1273 KB - resprot_v8i10e15303_app1.pdf]

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Abbreviations

BAT: Burnout Assessment Tool
GRR: generalized resistance resource
MBI: Maslach Burnout Inventory
RTW: return to work
SOC: sense of coherence
WUR: Wageningen University and Research

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Protocol

Modern Innovative Solutions to Improve Outcomes in Severe Asthma: Protocol for a Mixed Methods Observational Comparison of Clinical Outcomes in MISSION Versus Current Care Delivery

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Abstract

Background: Asthma that is poorly controlled and undertreated can progress to more severe disease that is associated with high levels of unscheduled care that requires high-cost therapy, leading to a significant health economic burden. The identification and appropriate referral to a specialist asthma service is also often delayed by several months or years because of poor recognition and understanding of symptom severity. Current severe asthma services may take several months to provide a comprehensive multidisciplinary assessment, often necessitating multiple hospital visits and costing up to £5000 per patient.

Objective: This study aims to evaluate whether a new service model could identify poorly controlled and potentially severe asthma much earlier in the patient pathway, and then compare clinical outcomes between this new care model with standard care.

Methods: Modern Innovative Solutions to Improve Outcomes in (MISSION) Severe Asthma is a novel service model developed by asthma specialists from Portsmouth and Southampton severe asthma services. MISSION Severe Asthma identified patients with poorly controlled disease from general practice databases who had not been under secondary outpatient care in the last 12 months or who were not known to secondary care. In 1- or 2-stop assessments, a thorough review of diagnosis, disease phenotype, and control is undertaken, and clinical outcomes collected at baseline.

Results: A variety of clinical outcomes will be collected to assess the service model. The results will be reported in February 2020.

Conclusions: This protocol outlines a mixed methods study to assess the impact on disease control, unscheduled health care usage, and quality of life in patients seen in the MISSION clinic compared with a closely matched cohort who declined to attend.

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KEYWORDS

asthma; diagnosis; community health services; drug therapy; epidemiology; asthma treatment

Introduction

Background and Rationale

The Burden of Disease

Asthma affects 5.4 million patients in the United Kingdom with the majority of costs (nearly 80%) relating to treating poorly controlled asthma, amounting to over £1 billion per annum as a direct cost and an indirect cost to society (time off work and lost productivity) of £6 billion. In the past year, the Wessex Region has seen over 1800 emergency adult hospital admissions because of asthma (over 300 more than expected based on the national average), costing over £2.1 million to the local health authority.

Asthma UK highlights that over half of the people with asthma suffer debilitating symptoms despite being prescribed treatment [1]. Poorly controlled disease leads to exacerbations necessitating unscheduled care and high-cost medications while impairing a patient's quality of life and increasing the risk of premature death. In 2009, there were 1131 deaths because of asthma in the United Kingdom, triggering a Department of Health–commissioned National Audit of Asthma Deaths [2]. Reviews of asthma deaths have confirmed that those with the most severe, frequently exacerbating disease are at greatest risk of death. The Outcome Strategy for Chronic Obstructive Pulmonary Disease and Asthma recognized this huge burden on both patients and the National Health Service (NHS) and outlined the political commitment to improve asthma control and reduce asthma-related emergency health care needs and deaths [3]. Asthma UK also highlighted the need to improve the quality of life of people with asthma by improving access to services, reducing inequalities in care, and ensuring a high standard of care. It is accepted that the proactive clinical review of people with asthma improves clinical outcomes and the majority with poorly controlled asthma can achieve good control. The recent publication "NHS five-year forward view" identifies the traditional separation of primary and secondary care being a barrier to the integrated care that patients with chronic disease require [4].

The Unmet Need

The Specialised Services Pathway for Severe Asthma recognizes the burden of uncontrolled disease ordinarily amenable to antiinflammatory medications and the progression to longer term "severe" disease, necessitating high-cost therapies (e.g. bronchial thermoplasty) [5]. The identification and appropriate referral to a specialist asthma service is often delayed by several months or years because of poor recognition and understanding of symptom severity.

Current severe asthma services may take several months to provide a comprehensive multidisciplinary assessment often necessitating multiple hospital visits and costing up to £5000 per patient. The report "Fighting for Breath" highlighted these issues with service delivery recommending that referral pathways to severe asthma services should be improved [6].

Description of Clinical Intervention and Treatment

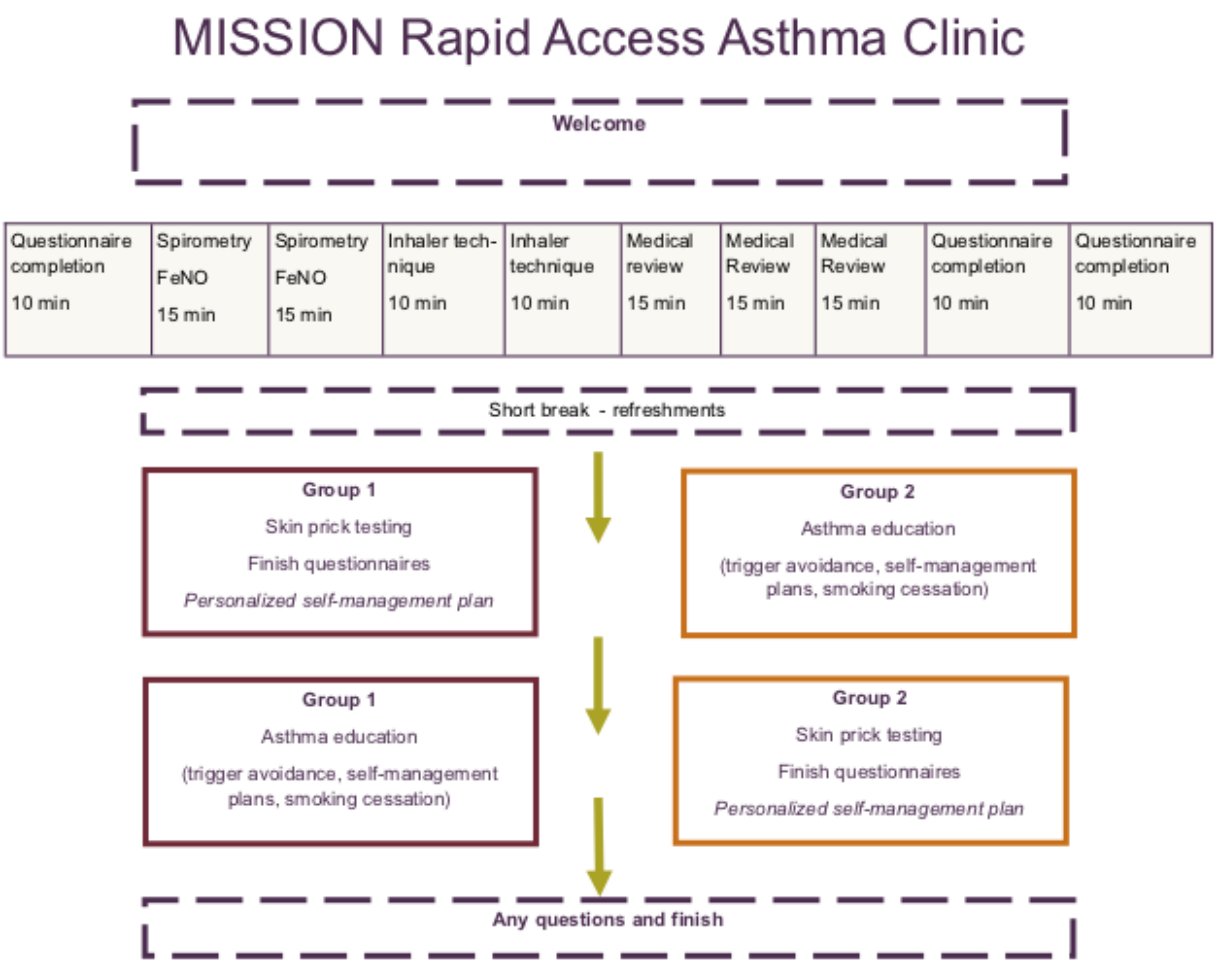
Modern Innovative Solutions to Improve Outcomes in (MISSION) Severe Asthma is a novel service model pilot that took place in June and July 2014. MISSION was developed by asthma specialists from Portsmouth and Southampton asthma services.

The MISSION concept involved a "carousel clinic" which brings together all the assessments and investigations a patient requires into one clinic—the patient moved around each assessment or "investigation station" in a serial fashion. This allowed the research team to efficiently gather all the data required for both staff and the patient. This severe asthma patient journey was mapped and opportunities for improvement were identified such as earlier diagnosis by active case finding of at-risk patients, followed by a swift multidisciplinary assessment which meant patients could be seen sooner and assessed more effectively. Patients attending standard outpatient services undergo basic lung function, chest x-ray, and medical review. They are then referred for other tests or specialist opinions as required at different time-points

MISSION Severe Asthma identified patients with poorly controlled disease from general practice (GP) databases who had not been under secondary outpatient care in the last 12 months or who were not known to secondary care. The patients were then invited to Rapid Access Asthma Clinics (RAACs) for assessment at their GP surgery on a Saturday, at a time convenient for them. The clinics were held on Saturdays at a time better suited to the needs of asthma patients, many of whom are working or studying full-time.

The RAAC delivered a comprehensive asthma review including assessments of allergic status, airway inflammation, education, self-management planning, and smoking cessation leading to a written personalized 1-year asthma management plan for their GP providing clear treatment recommendations for those with uncontrolled but treatable asthma (see Figure 1). Treatment recommendations were in line with current asthma guidelines.

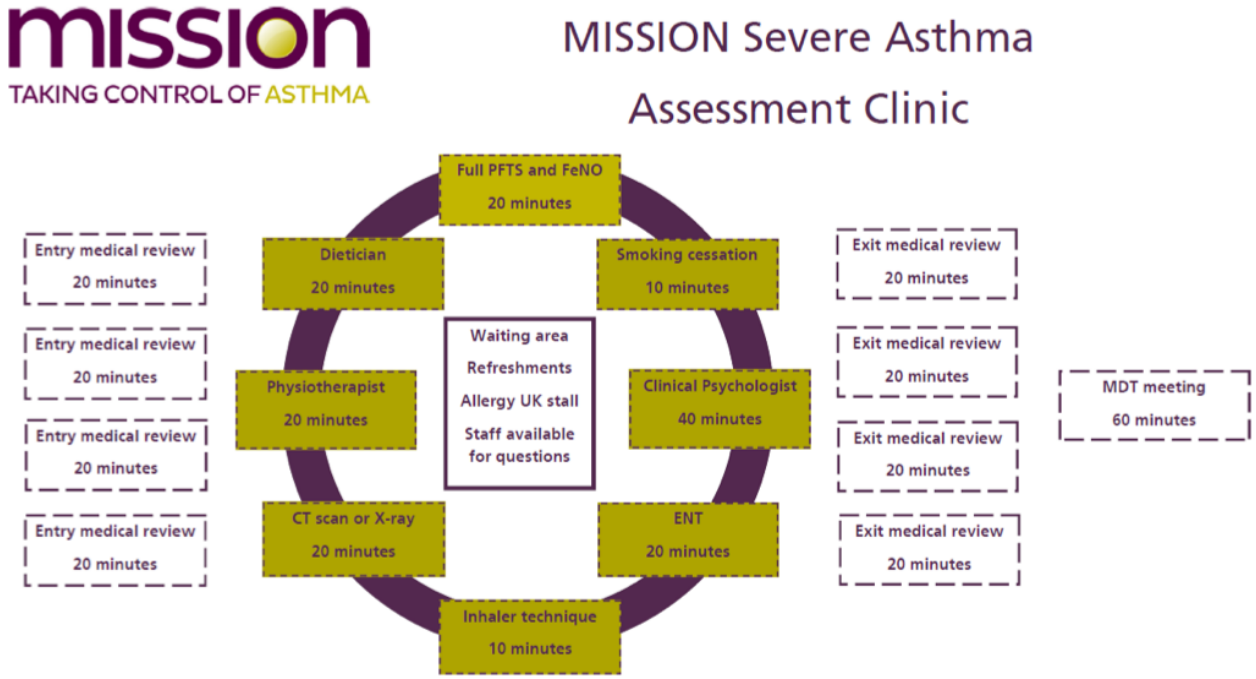
Figure 1. MISSION Severe Asthma Rapid Access Asthma Clinic flow chart. MISSION: Modern Innovative Solutions to Improve Outcomes.



At the end of the RAAC, a multidisciplinary team (MDT) meeting was held and treatment plans were discussed. The possible outcomes for patients included increasing or decreasing medication, referral for research study, referral to other medical teams, or a need for further assessment as the patient has potentially severe and uncontrolled asthma. Patients with potentially severe and uncontrolled asthma were invited for a more detailed multidisciplinary specialist assessment at a Severe Asthma Assessment Clinic (SAAC) again on a Saturday, held at Queen Alexandra Hospital.

MISSION SAAC included multidisciplinary assessment respiratory specialists, dieticians, physiotherapists, ear, nose, and throat (ENT) consultants, physiologists, psychologists, and pharmacists. Computed tomography (CT) scanning of the chest and sinus as well as flexible nasendoscopy to assess for sinus change and nasal polyps was available on that day. Patients saw the appropriate specialists based on the clinical history from the RAAC and a medical assessment on arrival to the SAAC. This ensured full lung function, inhaler technique, and medical exam for all patients, and physiotherapy, dietician, ENT, CT chest or sinus were performed where needed (see Figure 2). Representatives from Allergy UK also attended the clinic and provided advice and support to patients who were interested.

Figure 2. MISSION Severe Asthma Rapid Access Asthma Clinic flow chart. CT: computed tomography; ENT: ear, nose, and throat; FeNO: fractional exhaled nitric oxide; MDT: multidisciplinary team; MISSION: Modern Innovative Solutions to Improve Outcomes; PFT: pulmonary function test.



At the end of the clinic, a full MDT meeting was held to discuss each case. Patients and their GP received a detailed letter with all the test results and treatment changes as well as plans for follow-up. Follow-up referrals were made to specialists as needed, and treatment changes were made on the day of the clinic visit with support from the pharmacy for new treatment prescriptions.

In summary, the difference of the MISSION clinic from standard care was in 2 areas: First the active case finding of patients who are not already known to secondary care but are potentially uncontrolled. The second is the model of the clinic. Patients seen at the RAAC only will undergo more extensive testing and review of their asthma than primary care can provide and will have their comorbidities identified, asthma phenotyped, and treatment changes made appropriately.

Rationale for Study and Potential Impact

MISSION is a new and novel way of delivering highly specialized asthma care and has the potential to change the way asthma care is delivered across the United Kingdom as well as services for other long-term health conditions. The MISSION model is the first model of this type, and this study aimed to evaluate its success and compare the MISSION service with current care delivery. This will be done in several different ways. The study is a mixed methods evaluation of the new service comparing outcomes before and after the MISSION clinic using retrospective data analysis and prospective qualitative interviews. A control arm of patients not exposed to, but eligible for, the new MISSION clinic will also be included.

Objectives

Using quantitative and qualitative methods, our objective is to explore the impact of the MISSION service on clinical outcomes and patient experience. Using quantitative methods, we will (1) retrospectively analyze data collected as part of routine clinical care from all patients attending MISSION e.g. asthma control, medication usage and technique, exacerbations, comorbidities, allergies, and investigations (blood tests, radiological imaging, and nasendoscopy) and (2) retrospectively compare the assessment of comorbidities, investigations, and treatments between MISSION SAAC patients and standard outpatient care.

Primary Objectives

The primary objectives of this study are as follows:

1. To assess whether asthma control (assessed by exacerbation history, Asthma Control Questionnaire (ACQ), health care utilization, and short-acting beta-agonist (SABA) usage) is improved in MISSION SAAC patients compared with patients undergoing standard outpatient secondary asthma care at 6 months.
2. To assess whether asthma control (assessed by exacerbation history, health care utilization, and SABA usage) is improved in MISSION RAAC patients compared with those who were eligible for MISSION but did not attend.
3. To assess whether asthma control (assessed by exacerbation history, health care utilization, and SABA usage) is improved after attending the MISSION RAAC and SAAC.

Secondary Objectives

1. To conduct a prospective qualitative study exploring patients' experience, understanding and perceptions of their asthma as well as views on MISSION.

2. To explore the acceptability of MISSION as a service model for patients, staff, and the NHS.
3. To retrospectively compare a clinical case finding approach in primary care with a computer-assisted interrogation on primary care records.
4. To assess the health economic impact of the MISSION service.
5. To phenotype patients with uncontrolled or severe asthma in primary care and gain more information about the asthma population in Wessex.
6. To assess whether asthma comorbidities are assessed in standard outpatient care.
7. To assess waiting times and times to specialist referral in MISSION and standard outpatient care.

Methods

Study Design

A mixed methods observational study evaluating the new service, comparing outcomes before and after the intervention, and including a control arm of patients not exposed to, but eligible for, the new intervention is included. This will include analyses of the MISSION participants (attending both the RAAC and SAAC clinics), patients from the existing asthma service (from outpatient severe asthma clinics), and data from patients on GP records who were eligible to attend MISSION but did not (primary care patients). Finally, qualitative methods will be used to explore participant and health care professionals' views on MISSION. Multimedia Appendix 1 summarizes the participants journey and the different populations under study.

The MISSION Severe Asthma project has not been designed as a randomized controlled trial (RCT) but designed to evaluate a novel service model (the intervention) in participants with uncontrolled and potentially severe asthma, to assess whether it is deliverable and acceptable by participants and health care professionals, and to explore the barriers that would need to be addressed before a larger RCT.

A patient advisor reviewed all patient-facing documentation for the study and will give advice and feedback on the structure of the qualitative interviews.

Study Participants

Participants with uncontrolled or potentially severe asthma were identified from GP records by the MISSION team and new referrals to an asthma specialist clinic at Queen Alexandra Hospital between May and August 2014.

Study participants for qualitative interview will be recruited from patients who attended MISSION SAAC days and staff who attended MISSION RAAC or SAAC days. Qualitative one-to-one interviews will be held over the telephone.

Data for quantitative analysis will be collected from records made by the clinical team during the MISSION RAACs and SAACs and asthma outpatient clinics. GP records will be entered as usual by the GP. No extra data will be collected.

Eligibility Criteria

The participant must meet all of the following criteria to be considered eligible for the study:

- Male or female, aged 18 years or older.
- Is in one of the following population groups:
  - Attended the MISSION RAAC or
  - Attended the MISSION SAAC or
  - Identified as uncontrolled asthma by record searches and invited to the MISSION RAAC but did not attend "primary care patients" or
  - Has been referred to the specialist asthma clinic at Queen Alexandra Hospital "outpatient severe asthma patients" or
  - Attended the MISSION RAAC or SAAC as a health care professional
- Participant is willing and able to give informed consent for participation in the study.

Primary and Secondary Endpoints and Outcome Measures for Quantitative Study

Primary Outcome Measure for All Patients

The primary endpoint is asthma control as measured by exacerbation frequency (defined as deterioration in symptoms requiring ≥30 mg prednisolone or equivalent for ≥3 days).

Secondary Outcome Measures for Modern Innovative Solutions to Improve Outcomes in Severe Asthma Assessment Clinic Patients and Outpatient Severe Asthma Clinic Patients

1. SABA use measured by the number of inhalers prescribed in 6 months pre- and post-MISSION or outpatient clinic.
2. Exacerbation frequency (defined as deterioration in symptoms requiring ≥30 mg prednisolone or equivalent for ≥3 days) in 6 months pre- and post-MISSION or outpatient clinic.
3. Health care usage costs for asthma and number of contacts (GP visits, emergency department [ED] or out-of-hour [OOH] attendances, hospital admissions, and emergency GP visits) over 6 months pre- and post-MISSION or outpatient clinic.
4. Assessment of comorbidity (rhinosinusitis, anxiety and depression, dysfunctional breathing, gastro esophageal reflux, and obstructive sleep apnea) and method of assessment.
5. Assessment of inhaler technique and recommendations for inhaler devices.
6. Smoking cessation advice.
7. Investigations performed during 6 months in secondary care, for example, full lung function, sputum induction, and performing a high-resolution CT scan of the chest.
8. Time from GP referral to first clinic visit in secondary care.
9. Time between first and second visit in secondary care.
10. Time to appointment with other specialists for asthma-related comorbidity where indicated, for example, dietician, ENT, physiotherapist, psychologist, and CT imaging.

11. Assessment of eosinophilic airways inflammation through measurement of fractional exhaled nitric oxide (FeNO).
12. The frequency of nonattendance at clinic.

Secondary Outcome Measures for Modern Innovative Solutions to Improve Outcomes in Rapid Access Asthma Clinic Patients

1. SABA use measured by the number of inhalers prescribed in 6 months pre- and post-MISSION clinic.
2. Exacerbation frequency (defined as deterioration in symptoms requiring ≥30 mg prednisolone or equivalent for ≥3 days) during the 6 months pre- and post-MISSION.
3. Frequency and severity of comorbidities.
4. Frequency and type of allergy.
5. Measurement of exhaled nitric oxide.
6. Measurement and variation of lung function.
7. Frequency and type of additional asthma control medication.
8. Disease control and quality of life as assessed by ACQ and Asthma Quality of Life Questionnaire (AQLQ).
9. Number of patients having measurement of forced expiratory volume in 1 second (FEV1)÷forced vital capacity (FVC) as a proxy for asthma control and severity.

Secondary Outcome Measures for Modern Innovative Solutions to Improve Outcomes in Rapid Access Asthma Clinic Patients and Primary Care Patients

1. Prescription of SABAs during last 6 months at baseline and 6 months.
2. Exacerbation rates (defined as deterioration in symptoms requiring ≥30 mg prednisolone or equivalent for ≥3 days) during the last 6 months at baseline and 6 months.
3. ED attendances, OOH contacts, and hospital admissions during the last 6 months at baseline and 6 months.
4. Inhaled steroid doses and usage.
5. Number of patients having measurement of FEV1÷FVC as a proxy for asthma control and severity.
6. The sensitivity and specificity of the PRIMIS (Primary Care Information Services, University of Nottingham) Asthma Audit Tool in identifying the patients compared with gold standard specialist assessment and interrogation of primary care records.

Screening and Enrollment

Quantitative

All patients from the RAACs and all primary care patients will be approached for consent to use their anonymized data from the MISSION clinics or from GP records for research purposes. No extra data for research purposes will be collected for the quantitative analysis from patients at MISSION assessments, asthma outpatient clinics, or GPs.

Qualitative

Patients

All patients who attended MISSION SAACs will be approached to take part in qualitative one-to-one telephone interviews.

Health Care Professionals

Health care professionals who worked at the MISSION clinics from both primary and secondary care will be approached for qualitative interview. All health care professionals will be approached with an estimated 10 to be interviewed from primary care and 10 from secondary care. They will be contacted by email or telephone and, if interested, they will be sent a written information sheet by email or post. They will also be given contact details if they have any further questions regarding what is required to take part. If willing to take part, they will be sent a consent form to fill in and return to the study team.

Recruitment

Modern Innovative Solutions to Improve Outcomes in Rapid Access Asthma Clinic and Severe Asthma Assessment Clinic Patients

All patients who attended the MISSION RAACs (quantitative) and SAACs (quantitative and qualitative) will be contacted by telephone to discuss the study and then, if they are interested, will be sent a patient information sheet (PIS) and consent form with a covering letter.

If the patient is unable to be contacted by telephone, they will be sent a covering letter from the MISSION team inviting them to take part in the study. They will be provided with a number to contact if they have any questions. They will be given the opportunity to read the PIS, and if they agree to take part in the study, they can return the consent form by post in a stamped addressed envelope.

Primary Care Patients

Patients in primary care will be contacted as described above.

Outpatient Severe Asthma Patients

Patients who attended outpatient clinics as new referrals in June and July will be approached by telephone after being identified from the clinic attendance list. If the patient is willing, they will be sent a PIS and consent form to send back to the study team in a stamped addressed envelope.

Health Care Professionals

Health care professionals who attended the MISSION RAACs or SAACs will be contacted by email or telephone to explain the study and then sent a PIS by email or post if they are interested in taking part. They will be given time to read the PIS, and if they wish to take part, they will be asked to return a consent form in a stamped addressed envelope.

Quantitative Data Collection

Retrospective notes review at 6 months after the MISSION clinics will be performed to collect the following data. Data collected by study group are detailed in Table 1. Where information is not written in medical notes or clinic letters, it will be marked as not assessed.

Table 1. Schedule of procedures at the Severe Asthma Assessment and Rapid Access Asthma Clinics.

Study group	MISSION[a] Severe Asthma Assessment Clinics and outpatient severe asthma	MISSION Rapid Access Asthma Clinics and primary care patients
Full medical and asthma history	✓[b]	✓
Lung function testing	✓	✓
Inflammometry	✓	✓
Medication history	✓	✓
Health care usage (general practitioner attendances, emergency department attendances, and admissions)	✓	✓
Allergy status	✓	✓
Smoking status and history	✓	✓
Inhaler technique before and after review and documentation of improvements made	✓	✓
Disease-specific scores: Asthma Control Questionnaire and Asthma Quality of Life Questionnaire	✓	✓
Comorbidity screening: Epworth Sleepiness Scale, Sino Nasal Outcome Test -22, Hospital Anxiety and Depression Scale, Gastroesophageal Reflux Disease Questionnaire, and Nijmegen	✓	✓
Reviews by wider asthma multidisciplinary team, including time from referral to review	✓	X[c]

[a]MISSION: Modern Innovative Solutions to Improve Outcomes.

[b]✓: assessment performed.

[c]X: assessment not performed.

Modern Innovative Solutions to Improve Outcomes in Severe Asthma Assessment Clinic Patients and Outpatient Severe Asthma Patients

Retrospective notes review at 6 months after the MISSION clinics will be performed to collect the following data for MISSION SAACs and asthma outpatients. The clinical record form used for the MISSION SAACs is shown in Multimedia Appendix 2.

Where information is not written in medical notes or clinic letters, it will be marked as not assessed. Information will include the following:

- Medical history including asthma history, asthma triggers, allergy history, past medical history, family history, and occupation.
- Lung function including peak flow, FEV1, FVC, transfer factor of the lung for carbon monoxide, CO transfer coefficient, and FeNO.
- Medication history including asthma and non-asthma medication.
- Exacerbation history including number of steroid courses, hospital admissions, and intensive treatment unit admissions.
- Health care usage including nonroutine GP attendances, OOH contacts, and ED attendances in 6 months pre- and post-MISSION SAAC or outpatient clinic.
- Allergy testing results and whether done.
- Smoking status, and if current smoker, whether any smoking cessation advice or referral was done.
- Inhaler technique—whether checked, any improvements made, and recommendations for inhaler devices.
- Investigations performed and time in days after first visit.
- ACQ score.
- AQLQ score.
- Sino nasal outcome test-22 (measure of sino nasal symptoms) score.
- Epworth sleepiness score (measure of somnolence, which can be caused by obstructive sleep apnea).
- Hospital anxiety and depression scale score.
- Nijmegen (assessment of hyperventilation syndrome) score.
- Gastroesophageal Reflux Disease Questionnaire (assessment of gastroesophageal reflux) score.
- Time of GP referral, first clinic visit, and second clinic visit.
- Time of referral and appointment with other specialities, for example, ENT, dietician, and physiotherapy.

Modern Innovative Solutions to Improve Outcomes in Rapid Access Asthma Clinics

- Lung function including FEV1, FVC, peak flow, and FeNO.
- ACQ and AQLQ at baseline, 3 months, and 6 months in MISSION RAAC patients.
- Medication history for the last 12 months.
- Exacerbation history for the last 12 months.
- OOH, hospital, and emergency department attendances

Qualitative Data Collection

Modern Innovative Solutions to Improve Outcomes Severe Asthma Assessment Clinic Patients

The target population for the qualitative telephone interviews is all of the 20 patients who attended the MISSION SAACs. All patients in this group will be approached for an interview. Participants from MISSION SAACs who are taking part in qualitative interviews will have 1 telephone interview as part of this evaluation research study.

Interviews will be arranged at a mutual date and time of convenience. The researcher will make the telephone calls to minimize costs to the participants and facilitate audio recordings. Interviews will be held in a semistructured manner using a topic guide with relevant prompts. This will allow patients to focus discussion on the issues important to them and hear their experiences and views in their own words with free discussion guided by the patient.

The areas explored will include the patients' perceptions, understanding, fears, and concerns about their asthma as well as their views on MISSION—problems, barriers, and positive experiences. The interview will explore asthma and asthma service delivery.

The topic guide will be developed in conjunction with the payment protection insurance advisor.

Health Care Professionals

Telephone interviews will also be held with medical staff from both primary and secondary care who worked at the clinics. The anticipated number of participants will be 10 from primary care and 10 from secondary care. All staff who attended the MISSION clinics will be approached for consent. The interviews will explore the health care professionals' thoughts on MISSION and its strengths and weaknesses as well as any suggestions for improvement. The interviews will also explore the health care professionals' understanding and training in severe asthma and any areas where they would wish to see improvement.

Interview Structure

The semistructured interviews will be conducted by telephone and audio-recorded with notes taken. Telephone interviews have been chosen as participants live over a wide geographical area, and it will allow flexibility with interview times to accommodate participants' work and other commitments.

The interviews will be conducted by one of the health care professionals involved in the clinic. By having an existing relationship with the study participants and by the interviewer being a health care professional, the participant may be more willing to share experiences and personal views [7,8]. The researcher will be aware of the potential conflict with the professional role and the role as interviewer and will ensure open questions are asked [9]. The skills required during a clinical consultation have considerable overlap with the skills in qualitative interview [7,9]. It is important that the relationship between the interviewer and interviewee is clear when planning the qualitative interview [10] as it is recognized that this can be a factor in the interview.

At the beginning of the interview, patient participants will be reminded that the interview topic guide can be deviated, that they are free to suggest topic areas relevant to their experience and tell their experiences in their own words, and that there are no right or wrong answers but to share with the interviewer their thoughts, both the positives and negatives about MISSION, living with asthma, and asthma care.

There is also a concern that the patient participants may raise health questions or ask for health care advice. This will be addressed by explaining at the beginning of the interview that the interview is not a clinical consultation; however, any questions can be answered at the end of the interview.

Interview Analysis

The interviews will be digitally audio-recorded and transcribed by a professional transcription company. The data will be entered into a software program to facilitate qualitative analysis (NVivo10, QSR International (UK) Ltd, London, UK). All participants' names will be removed from the transcripts to retain confidentiality. When writing the results, no quotes will be directly attributed to participants. Participants will be given the opportunity to read and approve the transcript. The transcript will be sent to participants, and if no response is heard within 2 weeks, the transcript will be included in the analysis.

The results from the interview will be analyzed using a thematic and framework analysis, which uses a 5-step approach to analyzing and writing up data [11]. This involves familiarization with the interviews, identifying themes, indexing the themes onto the interview transcripts, charting, and mapping the themes. The themes from the patient and health professionals' interviews can be compared. This will enable key themes to be systematically identified and to map the themes from the patients against those from the health care professionals. A random sample of 5 interviews will also be independently assessed by the supervisor to review the themes and analysis undertaken.

The interviews will take between 45 min to 1 hour to complete depending on what the participants share with the interviewer. The interview can be terminated at any point the participant wishes to stop, and this will not influence their subsequent treatment.

Sample Size

The study was powered to show a difference between the MISSION group and the primary care group for the primary outcome, exacerbation frequency. The sample size was based on an analysis of covariance (ANCOVA) approach, with the outcome being exacerbation frequency in the second 6-month period and with the exacerbation frequency in the first 6-month period being the covariate. Baseline data suggest a mean number of exacerbations for this group of 1.29, with an SD of 1.30. There is expected to be no change in exacerbation frequency between time periods for the primary care group, whereas it is anticipated that exacerbations in the MISSION group may reduce by 50% to 0.65 exacerbations. A correlation between the exacerbation rates in the 2 time periods of 0.5 is assumed. The primary care group will be larger, with an anticipated 3:1 ratio. To show a difference between groups with a 5% significance level and 90% power, it is calculated that 44

subjects in the MISSION group and 132 in the primary group are required.

Data Analysis

Description of Analysis Populations

All data collected will be analyzed. There will be an analysis of the MISSION and outpatient groups separately. We will analyze 4 groups of participants: (1) qualitative assessments in participants attending the severe clinic, (2) health professionals attending either of the rapid or severe clinics, (3) quantitative assessments between those attending the rapid clinic in primary care to those invited but did not attend, and (4) those who attended the severe clinic compared with those routinely attending the outpatient severe asthma clinics in hospital.

Analysis of Endpoints

The analyses will compare the study outcomes between the 4 study groups.

The primary outcome is exacerbation frequency. This outcome will be analyzed using ANCOVA, with the outcome variable being exacerbation frequency in the second 6-month period and the exacerbation rate in the first 6-month period treated as the covariate. Owing to the likely skewed distribution of the exacerbation frequency, it may be necessary to perform a log transformation of the outcome before analysis. Comparisons will be made overall between the 3 groups, and specifically between the MISSION group and each of the other 2 groups.

The analysis of secondary outcomes measured on a categorical scale during the second 6-month period will be compared between groups using Fisher exact test. Continuous variables will be compared between groups using analysis of variance, if found to be normally distributed, or the Kruskal-Wallis test, if not found to be normal.

Comparisons between groups will also be made accounting for the values during the first time period. ANCOVA will be used for continuous variables, whereas logistic regression will be used for binary outcomes.

Discontinuation and Withdrawal of Participants From Study Treatment

Participants may withdraw at any point in either the qualitative or quantitative aspects of the study.

Definition of End of Study

The end of study is the date of the last qualitative interview of the last participant.

Procedure for Dealing with Missing, Unused, and Spurious Data

All data collected will be included in the analysis.

Procedures for Reporting Any Deviation(s) From the Original Statistical Analysis Plan

The study will analyze observational data retrospectively, and so we do not anticipate any significant deviations as would be expected in a longitudinal study.

Interim Analysis and Criteria for Early Study Termination

No interim analyses will be performed.

Dissemination

Patient volunteers and patients who have taken part in the qualitative interviews will be invited to help with dissemination events. The results will be submitted for presentation at national conferences. There will also be reports on the Wessex Asthma Network website for patients and public to access [12]. All study participants will be given a summary of the study results in an appropriate format.

Results

Quantitative

The MISSION team screened GP records to identify uncontrolled asthmatics to invite to MISSION clinics. There were 369 patients identified who had one or more of the criteria that suggest uncontrolled or potentially severe asthma (high inhaled corticosteroid dose >500 mcg BDP (Beclomethasone Diproprionate) , 2 or more exacerbations in the last 12 months requiring steroids for more than 3 days, any hospital, ED or OOH contact in the last 12 months, and high SABA usage—>6 inhalers in the last 12 months or reduced lung function FEV1 ≤70%). All patients who were identified were approached for the MISSION project.

Modern Innovative Solutions to Improve Outcomes in Rapid Access Asthma Clinic Patients and Severe Asthma Assessment Clinic Patients

The MISSION service: The searches identified 1436 patients who were manually reviewed by the MISSION team and 460 patients met the criteria. All these patients were invited to the clinic; 125 were booked in, and 84 attended the RAACs, of whom 22 were identified for the SAACs.

Primary Care Patients

All patients identified by the GP search but who did not attend the MISSION clinics will be approached for the study to maximize the chance of getting the same number of participants to the number who consents from the MISSION group.

Outpatient Severe Asthma Patients

The severe asthma outpatient clinic at Portsmouth Hospitals NHS Trust sees 16 new referrals per month. The sample will be matched to the same as the number of patients attending the SAACs, that is, 20 patients. All new referrals to the asthma clinic who meet the inclusion criteria will be included until the sample size is reached.

Qualitative

All 20 patients from the MISSION SAACs will be approached for a qualitative interview. Furthermore, all clinical staff who attended the MISSION RAACs or SAACs will be approached for an interview with an anticipated number of 10 interviewed from primary care and 10 from secondary care.

Discussion

The clinical intervention has been performed and the study has been ethically approved by the Yorkshire & The Humber-Leeds East Research Ethics Committee (Reference 15/YH/0136) and sponsored by Portsmouth Hospitals NHS Trust. The results will be reported in February 2020.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The study flow chart showing participants' journey.
[PDF File (Adobe PDF File), 40 KB - resprot_v8i10e9585_app1.pdf]

Multimedia Appendix 2
The case record form used for the Modern Innovative Solutions to Improve Outcomes Severe Asthma Assessment Clinics.
[PDF File (Adobe PDF File), 245 KB - resprot_v8i10e9585_app2.pdf]

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Abbreviations

ACQ: Asthma Control Questionnaire
ANCOVA: analysis of covariance
AQLQ: Asthma Quality of Life Questionnaire
CT: computed tomography
ED: emergency department
ENT: ear, nose, and throat
FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GP: general practitioner
MDT: multidisciplinary team

MISSION: Modern Innovative Solutions to Improve Outcomes
NHS: National Health Service
OOH: out-of-hour
PIS: patient information sheet
RAAC: Rapid Access Asthma Clinic
RCT: randomized controlled trial
SAAC: Severe Asthma Assessment Clinic
SABA: short-acting beta-agonist

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Protocol

Hypothermic Oxygenated Machine Perfusion of Extended Criteria Kidney Allografts from Brain Dead Donors: Protocol for a Prospective Pilot Study

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Abstract

Background: Kidney transplantation is the only curative treatment option for end-stage renal disease. The unavailability of adequate organs for transplantation has resulted in a substantial organ shortage. As such, kidney donor allografts that would have previously been deemed unsuitable for transplantation have become an essential organ pool of extended criteria donor allografts that are now routinely being transplanted on a global scale. However, these extended criteria donor allografts are associated with significant graft-related complications. As a result, hypothermic oxygenated machine perfusion (HOPE) has emerged as a powerful, novel technique in organ preservation, and it has recently been tested in preclinical trials in kidney transplantation. In addition, HOPE has already provided promising results in a few clinical series of liver transplantations where the liver was donated after cardiac death.

Objective: The present trial is an investigator-initiated prospective pilot study on the effects of HOPE on extended criteria donor allografts donated after brain death and used in kidney transplantation.

Methods: A total of 15 kidney allografts with defined inclusion/exclusion criteria will be submitted to two hours of HOPE via the renal artery before implantation, and are going to be compared to a case-matched group of 30 patients (1:2 matching) who had kidneys transplanted after conventional cold storage. Primary (posttransplant dialysis within 7 days) and secondary (postoperative complications, early graft function, duration of hospital and intensive care unit stay, and six-month graft survival) endpoints will be analyzed within a six-month follow-up period. The extent of ischemia-reperfusion injury will be assessed using kidney tissue, perfusate, and serum samples taken during the perioperative phase of kidney transplantation

Results: The results of this trial are expected in the first quarter of 2020 and will be presented at national and international scientific meetings and published in international peer-reviewed medical journals. The trial was funded in the third quarter of 2017 and patient enrollment is currently ongoing.

Conclusions: This prospective study is designed to explore the effects of HOPE on extended criteria donor kidney allografts donated after brain death. The present report represents the preresults phase.

Trial Registration: Clinicaltrials.gov NCT03378817; https://clinicaltrials.gov/ct2/show/NCT03378817

(JMIR Res Protoc 2019;8(10):e14622) doi:10.2196/14622

KEYWORDS

hypothermic oxygenated machine perfusion; donation after brain death; extended criteria donor; kidney transplantation; kidney transplant; organ donation

Introduction

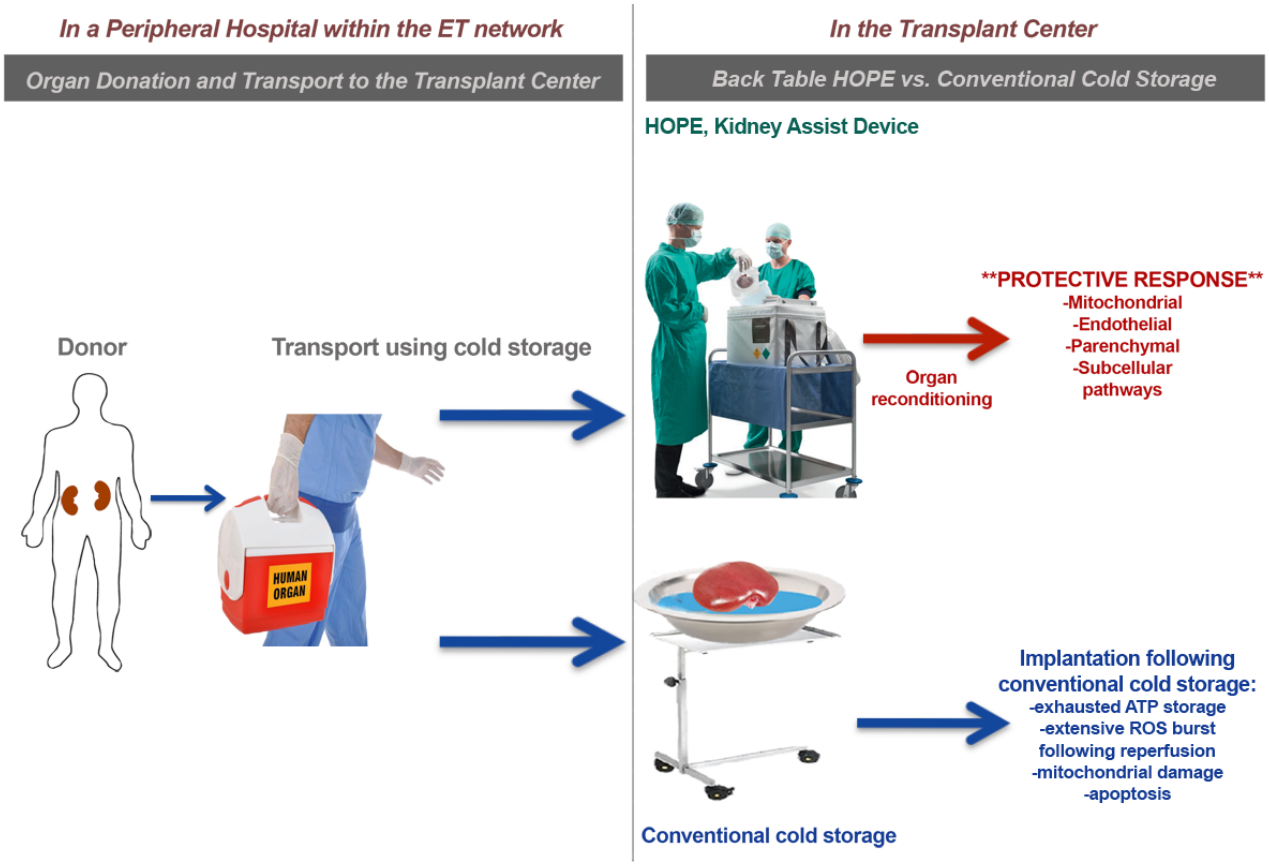
Since Joseph Murray's pioneering efforts in 1954, allogenic kidney transplantation has evolved as the standard treatment for end-stage renal disease [1]. In 2018, approximately 8000 patients were waiting for kidney transplant in Germany, but only 2005 transplant procedures using postmortem organs were performed due to organ scarcity [2]. Several strategies for donor pool expansion are being pursued concurrently. These include the use of old donors, living donors, and extended criteria donor (ECD) allografts for kidney transplant. However, ECD-allografts exhibit poor tolerance to ischemia-reperfusion injury (IRI), an important cause of kidney damage [3,4]. As such, IRI is usually the underlying cause of graft dysfunction in ECD kidney transplant [5]. Primary graft nonfunction, leading to graft loss and retransplantation, as well as delayed graft function (DGF) with the need for posttransplant dialysis are the most frequent clinical manifestations of this pathology [5].

Dynamic organ preservation approaches, such as machine perfusion, hold promise for improving organ preservation and resuscitation of marginal donor allografts [6-9]. Although tissue oxygen consumption is markedly decreased at 4-10°C, there is still relevant metabolism at this temperature. Oxygen during machine perfusion is the key ingredient in the protective responses of hypothermic oxygenated machine perfusion (HOPE), with organ reconditioning effectively increasing the cellular energy balance via various mitochondrial pathways [10]. Over time, the addition of oxygen during machine perfusion emerged as a powerful novel tool in organ preservation [11,12]. HOPE is an easy to implement, short-term, end-ischemic reconditioning concept, as the organ perfusion is performed in the transplant center shortly before the actual implantation [11,13]. Ischemia-reperfusion injury occurs upon revascularization of the kidney allograft. Decrease of oxidative metabolism and depletion of adenosine triphosphate (ATP) are the results of the lack of oxygen during ischemia. Reintroduction of oxygen to the ischemic allograft results in massive reactive oxygen species production and release, leading to cellular damage. The mechanisms behind IRI are multifactorial, and ways to minimize its detrimental effects are still the subject of intense debate [14].

In the preclinical setting, the positive effects of HOPE have recently been demonstrated through a reduction in the incidence of tubular damage, macrophage activation, and functional optimization of cellular energy-status in vitro and in vivo [8,9,11]. There are several hypotheses regarding the underlying mechanisms of HOPE-induced organ protection. According to these hypotheses, HOPE presumably exerts its positive effects by: (1) modulating cellular metabolism (energy balance, mitochondrial respiration, IRI); (2) stimulating the vascular endothelial layer; and (3) triggering various subcellular protective pathways (Figure 1) [15]. Investigating the effects of HOPE in a rat model, Kron et al recently demonstrated its beneficial effects on the immune response. Less cytokine release and less T-cell and macrophage activation were measured in the animals receiving the HOPE-treated kidneys [16]. Accordingly, decreased immune response may be one of the key underlying mechanisms of HOPE.

The aim of this prospective cohort study is to investigate the effects of HOPE on ECD kidney allografts donated after brain death. This study utilizes a comprehensive sample collection protocol to assess the subcellular mechanisms of HOPE in the clinical setting.

Figure 1. Hypothermic oxygenated machine perfusion. The donor organ is explanted and transported to the transplant center stored in a box of ice. In the transplant center, the kidney is connected to the Kidney Transport Assist device and HOPE is performed. It is assumed HOPE leads to less oxidative stress, decreased cell death and enhanced energy reserves. Adapted from Czigany et al [<xref ref-type="bibr" rid="29ref12">12</xref>]. ET: Eurotransplant, HOPE: hypothermic oxygenated machine perfusion; ATP: adenosine triphosphate; ROS: reactive oxygen species.



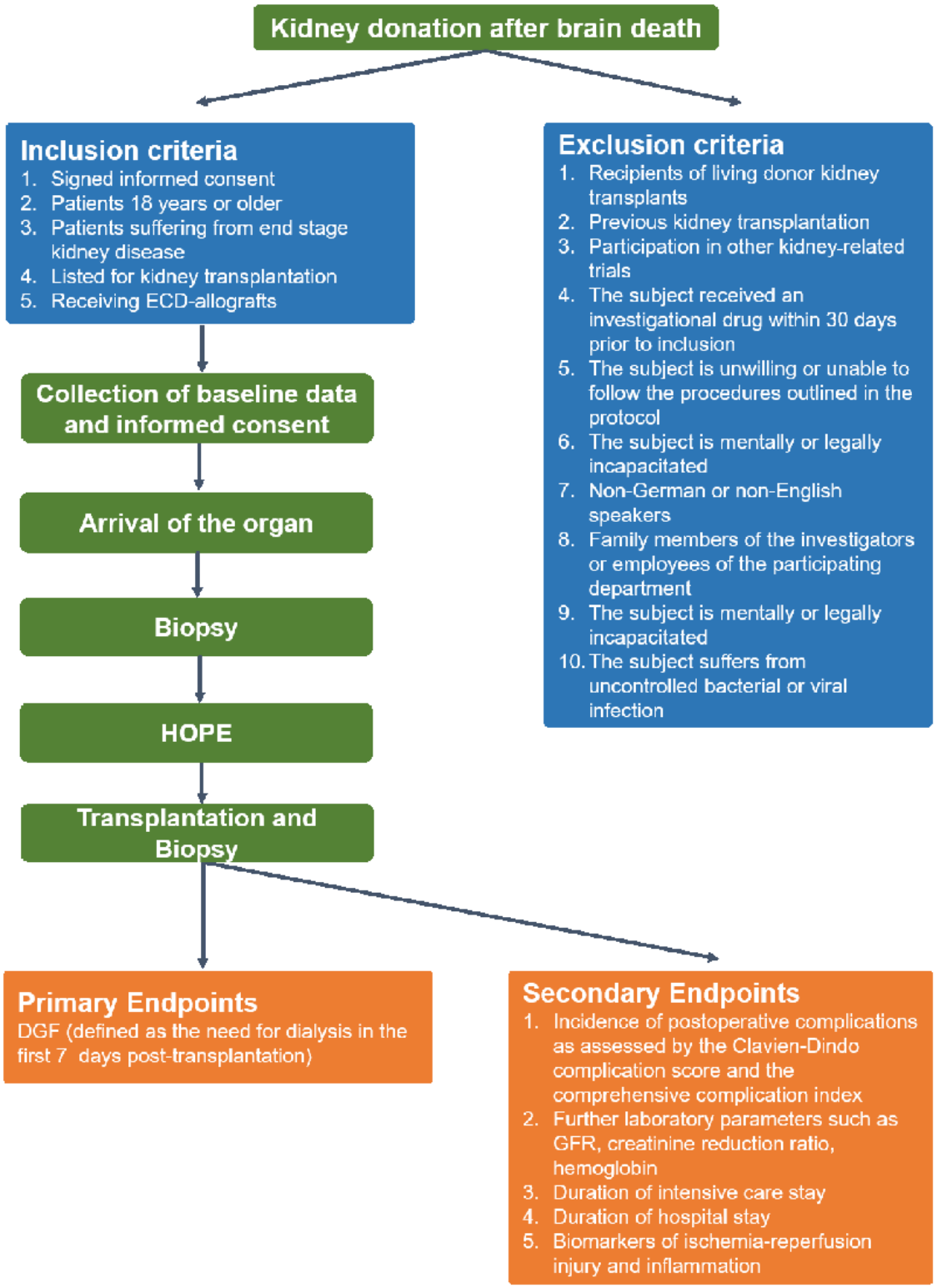
Methods

Study Type and Eligibility

The present trial is an investigator-initiated pilot study on the effects of HOPE on ECD-allografts in donated after brain death kidney transplants. Figure 2 summarizes the trial design.

Patients older than 18 years of age, suffering from end-stage renal disease (ESRD), listed for kidney transplant, and receiving ECD organs at the Department of Surgery and Transplantation, University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany, are eligible for the study. Informed consent was obtained from all subjects participating in the trial by a qualified member of the study team. Inclusion and exclusion criteria are listed in Textbox 1.

Figure 2. Study flow chart. ECD: extended criteria donor; HOPE: hypothermic oxygenated machine perfusion; DGF: delayed graft function; GFR: glomerular filtration rate.



Textbox 1. Study inclusion and exclusion criteria.

Inclusion Criteria:

- Signed informed consent
- 18 years or older
- Suffering from ESRD (end-stage renal disease)
- Listed for kidney transplant
- Receiving ECD (extended criteria donor)-allografts

Exclusion criteria:

- Recipients of living donor kidney transplants
- Previous solid organ transplantation
- Combined procedures (eg, kidney-liver transplantation)
- Participation in other kidney-related trials
- The subject received an investigational drug within 30 days prior to inclusion
- The subject is unwilling or unable to follow the procedures outlined in the protocol
- The subject is mentally or legally incapacitated
- Non-German or non-English speakers
- Family members of the investigators or employees of the participating department
- The subject suffers from uncontrolled bacterial or viral infection

Organ Procurement and Definition of Extended Criteria Donor Criteria

ECD kidney allografts will be retrieved by local procurement teams with the Eurotransplant network. Following cross-clamping (*in situ* flushing of the abdominal organs and the beginning of cold ischemia time), allografts will be removed and transported in a standardized fashion on packed ice. Required data regarding the donor and the organ will be collected and will be transferred to designated case report files (CRFs).

As per previous studies [4,17] deceased donors must be ≥60 years old, but it is possible for those aged between 50-59 years old to be donors if they have at least two of the following conditions: (1) cerebrovascular cause of death; (2) serum creatinine greater than 1.5 mg/dL (132.6 µmol/L); or (3) history of arterial hypertension.

Hypothermic Oxygenated Machine Perfusion Versus Historic Cold Storage Group

Primary and secondary outcomes of patients transplanted with the HOPE-treated kidneys will be compared to a case-matched group of 30 patients (1:2 matching) transplanted with ECD organs after conventional cold storage, using identical surgical techniques and perioperative treatment at the Department of Surgery and Transplantation, University Hospital RWTH Aachen. The present trial comprises two groups, a perfusion (Group 1, HOPE) and a control conventional cold storage group (Group 2, Historic). Patients on the waiting list for kidney transplant with proven written consent will be recruited. HOPE will be applied to the allograft in the operating room after regular organ procurement, transport, and back-table preparation (Figure 1).

We adapted a protocol based on clinical studies with nonoxygenated hypothermic machine perfusion, and on preclinical experience with HOPE [11,18,19]. HOPE will be applied through the renal artery for at least two hours, with a perfusion pressure of 25 mmHg and a perfusion rate of 50-200ml/min using 1 L of recirculated perfusate at 0-4°C. The perfusate will be oxygenated using medical grade oxygen (O^2), with a partial pressure of oxygen (pO^2) of 60-80 kilopascals (kPa), by an oxygenator included as a disposable part of the setup. Perfusion parameters registered by the device will be stored automatically and evaluated for possible patterns. Immediately prior to perfusion, grafts will be flushed with perfusate solution to wash out the residual histidine-tryptophan-ketoglutarate (HTK) solution. Storage, management, and use of the medical products will be carried out according to the manufacturer's guidelines.

Matching Criteria

Donor urine output over the last 24 hours before retrieval, cold ischemic time (CIT), and the recipients Charlson comorbidity index [20] have been selected as matching criteria. Matching will be performed using a propensity score [21].

Kidney Transplantation

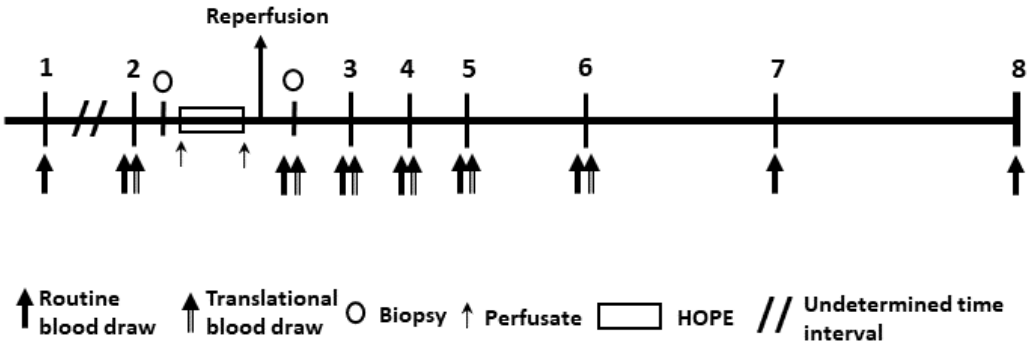
Kidney grafts will be implanted heterotopically to the iliac fossa, as per our institutional protocol. The renal vein is anastomosed first, end-to-side to the external iliac vein, followed by renal artery anastomosis to the external iliac artery in the same fashion. After reperfusion of the kidney, the ureter is implanted

into the bladder, according to Lich-Gregoir, and the uretero-cystostomy is stented with a 6-French double-J stent.

Sample Collection and Storage

Ischemia reperfusion injury will be assessed using kidney tissue samples taken upon arrival of the organ (before HOPE) and at the end of implantation after reperfusion, but before closure of the abdomen, to evaluate the extent of IRI (Figure 3). In total, two biopsies using BARD MONOPTY Disposable Core Biopsy Instrument (Bard Biopsy Systems Inc, Tempe, Arizona) will be harvested from the ECD kidney allograft and used for translational research. During machine perfusion, perfusate samples will be collected every 20 minutes. Blood samples are taken as part of the daily routine during the perioperative and postoperative course of kidney transplant (Figure 3). Blood parameters of kidney function (ie, creatinine, urea, estimated glomerular filtration rate [eGFR]) will be monitored. An additional 20 mL of blood will be drawn on postoperative days 1, 2, 3 and 7 and will be used for translational research (Figure 3). All kidney tissue, serum, and perfusate will be directly snap-frozen in liquid nitrogen (−80°C) and stored for 6 months after completion of the trial. To assess the subcellular mechanisms of HOPE in the clinical setting, various parameters, including markers of kidney injury (creatinine and neutrophil gelatinase-associated lipocalin (NGAL) in plasma samples), tissue ATP concentration, inflammatory mediators (eg, tumor necrosis factor alpha, interleukin-6, macrophage migration inhibitory factor, interleukin-10, monocyte chemoattractant protein-1), and biomarkers of oxidative damage (eg, 8-hydroxy-2'-deoxyguanosine), will be analyzed [11,12].

Figure 3. Interventions and study visits. Numbers represent the single study visit: Visit 1: screening, enrollment; Visit 2: admission; Visits 3, 4, and 5: postoperative days 1, 2, and 3; Visit 6: seventh postoperative day; Visit 7: discharge; Visit 8: 6 months follow-up; final visit. HOPE: hypothermic oxygenated machine perfusion.



Immunosuppression and Postoperative Care

All patients will be treated according to our institutional protocol. Aside from HOPE for the donor kidneys, all procedures, including peri- and intraoperative management, are conducted in accordance with standard surgical kidney transplant management. The applied immunosuppressive regimen is based on intraoperative induction therapy with intravenous methylprednisolone and either basiliximab or thymoglobulin followed by corresponding oral doses of prednisolone, tacrolimus, and mycophenolate mofetil.

Study Endpoints

The primary endpoint is DGF, which is defined as the need for dialysis in the first 7-days posttransplantation. The secondary endpoints of the study include: (1) duration of DGF (defined as the period between kidney transplant and last dialysis in days) and functional DGF (defined as <10% fall in serum creatinine for 3 consecutive days in the first week posttransplantation); (2) creatinine reduction ratio day 2 ([creatinine day 1−creatinine day 2]/creatinine day 1) and Creatinine reduction ratio day 5 ([pretransplant creatinine−creatinine day 5]/pretransplant creatinine); (3) incidence of postoperative complications, as assessed by the Clavien-Dindo complication score and the comprehensive complication index [22]; (4) duration of intensive care and hospital stay; (5) recipient and graft survival after six months; (6) renal function (assessed by serum creatinine and eGFR) at one-, three- and six-months post-transplant; and (7) basic and translational research, which involves assessing biomarkers from routinely harvested kidney tissue and serum following implantation to obtain information on kidney injury, extent of oxidative damage, redox- and energetic homeostasis of the implanted donor kidney.

Study Population

To the best of our knowledge, aside from a sole case of HOPE-treated dual kidney transplant reported recently, no experience of HOPE in human donation after brain death kidney transplant has been published yet [23]. In the present pilot study, 15 patients (N=15) will be treated with HOPE to gain first prospective clinical knowledge. HOPE-treated patients will be compared to a case matched group of 30 patients (N=30).

Data Collection and Statistics

Patients will be given consent forms while in our outpatient clinic. Data will be obtained using study specific CRFs completed by the members of the study team. Subjects will be informed about data protection, including pseudonymization.

Encoded data will only be provided to authorized persons (ie, authorized study staff, authorities, institutional review board). The study will be prematurely terminated for any individual subject in case of study-related complications or if the subject withdraws informed consent. Parametric and nonparametric tests will be done according to the normality of the data distribution. Two-way analysis of variance will be used for the time-course analysis of laboratory parameters. The log-rank test will be used for comparisons between Kaplan-Meier curves of six-month graft survival. Statistical significance will be defined as $P<.05$.

Safety Considerations

Exclusively certified medical products will be used. Blood sampling and tissue biopsies during the transplant procedure will be performed according to clinical standards, preventing any relevant study-related risks or additional burden on the subjects. An interim analysis will be performed as soon as 10 patients are HOPE-treated. The trial will be terminated immediately if the following criteria is fulfilled: significantly higher DGF rate ($P<.05$ using the Chi-squared test) in the HOPE group compared to the matched conventional cold storage group (efficacy).

Ethics

The present trial will be carried out in compliance with the current version of the Declaration of Helsinki, good clinical practice guidelines (International Conference on Harmonization-Good Clinical Practice [ICH-GCP]), and all national legal and regulatory requirements. The institutional review board of the University RWTH Aachen has approved the study protocol, including consent form and patient information leaflet (EK 184/17). Members of the study team have completed a course in good clinical practice as certified by the German Medical Chamber.

Study Group

The study group of the present trial comprises the trial sponsor (GL, UPN) and the principal investigator (GL) of the University Hospital RWTH Aachen

Ischemia-Reperfusion Injury and Inflammation

IRI is an inevitable event in organ transplantation. Reduction of oxygen delivery because of blood flow interruption leads to anaerobic metabolism and the production of oxygen-free radicals and oxidative stress as a respiratory burst at the onset of reperfusion. IRI plays a key role in DGF and primary graft nonfunction following kidney transplantation, depending on initial organ quality [8,9,24,25]. To detect the effects of HOPE on IRI, the kidney tissue, blood, and perfusate samples obtained in this study will be used to quantify several innovative parameters of inflammation (eg, interleukins, tumor necrosis factor-alpha), kidney injury (Cytatin-C, NGAL, etc) energy- (ATP levels) [11,26], and redox-threshold (Hemoxygenase-1, Malondialdehyde) [12,27]. Luminometry, Spectrophotometry, Luminex-assay, Enzyme-linked immunosorbent assay (ELISA), Reverse transcriptase polymerase chain reaction (RT-PCR) and Western blot will be used for these analyses. Proteomics and metabolomics analysis will be performed on kidney tissue samples to potentially identify early mediators of HOPE-mediated organ protection.

Results

Results of this trial will be presented at national and international scientific meetings and published in international peer-reviewed medical journals. The trial was funded in the third quarter of 2017. Patient enrollment is currently ongoing, and the first results are expected in the first quarter of 2020.

Discussion

Allogenic kidney transplantation has evolved as the mainstay of treatment for end-stage renal disease [3,28]. The decreasing availability of quality organs for transplantation has resulted in substantial organ shortage, and as such kidney donor allografts that would have previously been deemed unsuitable for transplantation have become an essential organ pool of ECD-allografts that are now routinely being transplanted on a global scale. However, the use of ECD allografts is associated with IRI and a higher incidence of primary graft nonfunction or DGF [5]. The restoration of blood flow after cold and warm ischemia leads to paradox via massive release of reactive oxygen species, cytokines, chemokines, and activation of leukocytes [29]. Although machine perfusion in kidney transplantation was explored in the 1970's, it has not been widely used over the last few decades. Due to technical improvements and the addition of oxygen during machine perfusion, HOPE has evolved into a promising novel tool in organ preservation [11,12]. The superiority of HOPE over nonoxygenated cold machine perfusion and conventional cold storage was recently demonstrated in some preclinical experiments as well as in clinical trials using HOPE in donation after cardiac death liver transplantation [11,12,15]. A recent kidney transplantation rodent model in vivo study by Kron et al compared conventional cold storage, normothermic oxygenated blood perfusion, HOPE, and hypothermic deoxygenated perfusion using nitrogenated perfusate, and demonstrated superior effects of HOPE on macrophage activation, endothelium activation, tubular damage, and graft function as compared to other preservation methods [11].

We identified four active clinical trials exploring the effects of HOPE in kidney transplantation. In a pilot study by Ravaoili et al, 20 subjects were recruited to receive either HOPE-treated ECD-kidney or ECD-liver allografts. Whether the organs used were donated after cardiac death or donated after brain death remains unclear (NCT03031067; Table 1). One trial (NCT02621281) is a large multi-center RCT investigating HOPE in donated after cardiac death kidney transplantation, including ECD and nonECD allografts in a large Chinese cohort. Two relevant trials of the Consortium for Organ Preservation in Europe are recruiting in a large collective of patients. The Cold oxygenated machine preservation of aged renal donation after cardiovascular death transplants (COMPARE) trial (ISRCTN32967929), initiated at the University Hospital Leuven, Belgium, included a total of 102 transplanted donated after cardiac death kidney pairs that are being used to discover whether continuous oxygenated machine perfusion is superior

to nonoxygenated machine perfusion. The COMPARE trial has a considerably different design compared to our study, with a logistically complex perfusion concept involving the transport of the machines to the retrieval center and applying continuous HOPE. Preimplantation oxygenated hypothermic machine perfusion reconditioning after cold storage (COPE-POMP) (ISRCTN63852508), initiated from the University Hospital of Essen, Germany, is currently ongoing and involves randomizing ECD allografts to end-ischemic preimplantation HOPE or to conventional cold storage.

Although we have designed our trial carefully, nonrandomization of the study groups and nonblinding of the transplant team, as well as matching with a historical group, are limitations of the present study. Nevertheless, conclusive clinical data about end-ischemic HOPE in human kidney transplantation are still missing and larger multi-center studies on this topic are currently underway. Therefore, it seems plausible to conduct this trial as a pilot study with a focus on short-term outcomes as well as translational research aspects of HOPE in ECD-kidney transplantation.

The present trial, nevertheless, possesses some specific strengths in that it focuses on patients solely receiving ECD-allografts, a population in which we anticipate the best cost/benefit ratio from the utilization of HOPE. Kidney transplant outcomes stem from a combination of various factors. Our matching criteria have been carefully selected based on previous clinical evidence to include both donor and recipient factors, which have a key role to play in posttransplant outcome [30,31]. Regarding translational research and sample collection, our study design as a single center prospective trial may also be beneficial. Samples will be obtained according to our study protocols and by the same study members throughout the whole study period. The results of the translational part of this study may deliver novel insights into the underlying subcellular effects of HOPE in human kidney transplantation.

Table 1. Active prospective clinical trials on HOPE (hypothermic oxygenated machine perfusion) in kidney transplants (as assessed on clinicaltrials.gov and isrctn.com on February 27, 2019).

Trial number	Study center	Study type	Enrollment	Donor group	MP[a] point of time
NCT03378817 (Present trial)	University Hospital Aachen, Aachen, Germany	CS[b]	15	ECD[c]-donated after brain death	End-ischemic
NCT03031067	University of Bologna, Bologna, Italy	CS	10	ECD (donated after brain or cardiac death unclear)	Unclear
NCT02621281	First Affiliated Hospital Xi'an Jiaotong University, Xi'an, Shaanxi, China	RCT[d]	400	donated after cardiac death	Immediately after retrieval
ISRCTN32967929	University of Leuven, Leuven, Belgium	RCT	210	donated after cardiac death	Immediately after retrieval
ISRCTN63852508	University Clinic Essen, Essen, Germany	RCT	262	ECD-donated after brain death	End-ischemic

[a]MP: machine perfusion.

[b]CS: cohort study.

[c]ECD: extended criteria donor.

[d]RCT: randomized controlled trial.

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Authors' Contributions

The initial study concept was derived from the initiating investigator study group: GL, FAM, ZC, and UPN. FAM, GL, and ZC drafted the manuscript. JB, JoB, IA, KR, DAMS, MM, PB, WR, and UPN participated in designing the study, preparing the revised protocol, and functioning as local investigators at the University Hospital RWTH Aachen. All authors read and approved the final version of the manuscript**.**

Conflicts of Interest

None declared.

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Abbreviations

ATP: adenosine triphosphate
CIT: cold ischemic time
COMPARE: cold oxygenated machine preservation of aged renal donation after cardiovascular death transplants
COPE-POMP: preimplantation oxygenated hypothermic machine perfusion reconditioning after cold storage
CRF: case report file
DGF: delayed graft function
ECD: extended criteria donor
eGFR: estimated glomerular filtration rate
ELISA: enzyme-linked immunosorbent assay
ESRD: end-stage renal disease
HOPE: hypothermic oxygenated machine perfusion
HTK: histidine-tryptophan-ketoglutarate
ICH-GCP: International Conference on Harmonization-Good Clinical Practice
IRI: ischemia-reperfusion Injury
kPa: kilopascal
MPS: machine perfusion solution
NGAL: neutrophil gelatinase-associated lipocalin
O2: oxygen
pO2: partial pressure of oxygen
RWTH: Rheinisch-Westfälische Technische Hochschule

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Corrigenda and Addenda

Correction: Wearable Digital Sensors to Identify Risks of Postpartum Depression and Personalize Psychological Treatment for Adolescent Mothers: Protocol for a Mixed Methods Exploratory Study in Rural Nepal

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Related Article:

Correction of: https://www.researchprotocols.org/2019/9/e14734/

(JMIR Res Protoc 2019;8(10):e16837) doi:10.2196/16837

In “Wearable Digital Sensors to Identify Risks of Postpartum Depression and Personalize Psychological Treatment for Adolescent Mothers: Protocol for a Mixed Methods Exploratory Study in Rural Nepal” by Poudyal et al (JMIR Res Protoc 2019;8(9):e14734), a minor error in the typesetting stage of publication resulted in the International Registered Report Identifier (IRRID) not being included in the final version of the article.

The IRRID “DERR1-10.2196/14734” has now been added to the paper.

The correction will appear in the online version of the paper on the JMIR website on October 30, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Viewpoint

Writing a Systematic Review for Publication in a Health-Related Degree Program

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Abstract

Background: The protocol in this manuscript was designed to help graduate students publish. It is the result of a challenge from our provost in 2013. I developed this protocol over the last 6 years and have exercised the protocol for the last 5 years. The current version of the protocol has remained mostly static for the last 2 years—only small changes have been made to the process.

Objective: The objective of this protocol is to enable students to learn a valuable skill of conducting a systematic review and to write the review in a way that can be published. I have designed the protocol to fit into the schedule of a traditional semester, but also used it in compressed semesters.

Methods: An image map was created in HTML 5.0 and imported into a learning management system. It augments traditional instruction by providing references to published articles, examples, and previously recorded instructional videos. Students use the image map outside the classroom after traditional instruction. The image map helps students create manuscripts that follow established practice and are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and whose authorship follows guidelines by the International Committee of Medical Journal Editors.

Results: Since its inception, this protocol has helped 77 students publish 27 systematic reviews in nine journals worldwide. Some manuscripts take multiple years to progress through multiple review processes at multiple journals submitted in sequence. Two other professors in the School of Health Administration have used this protocol in their classes.

Conclusions: So far, this method has helped 51% of graduate students who used it in my graduate courses publish articles (with more manuscripts under consideration whose numbers have remained uncounted in this sum). I wish success to others who might use this protocol.

(JMIR Res Protoc 2019;8(10):e15490) doi:10.2196/15490

KEYWORDS

systematic review; health information management

Introduction

Background

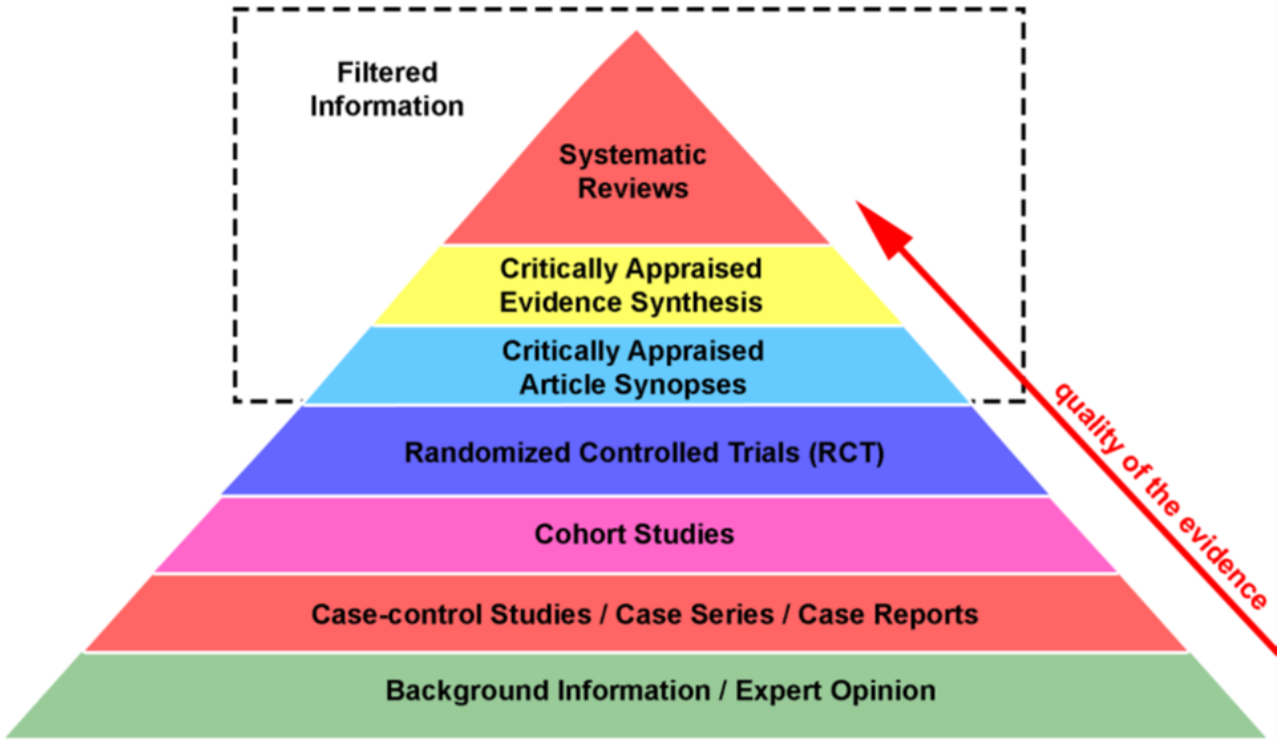
Responding to a challenge by our provost to help our graduate students publish, I created this protocol to conduct and write high-quality systematic reviews that would not only serve as springboards to larger research, but also be publishable on their own. With this protocol, I created a process map to define each step. From the process map, I created an image map in HTML 5 (Multimedia Appendix 1) to be hosted online. The image map is hosted by Texas State University's learning management system (LMS) and integrated into courses. It contains helper videos, articles, and examples to help guide the students outside the classroom. My process has been integrated into multiple courses at both the graduate and undergraduate levels. Between semesters, I enter into partnership with those graduate students whose work is of high quality and also research viable topics

for the following term. With this protocol, I have helped 77/151 (51%) graduate students publish 27 systematic reviews [1-27] (two in press) in nine high-quality journals worldwide over the last 5 years: Journal of Medical Internet Research [2,4,8-11,14,15,17,18,26], Journal of Medical Systems [19,20,23,24], Journal of Telemedicine and Telecare [3,22], Technology and Healthcare, [5,6], BMJ Open [16,21], JRSM Open [12], Applied Clinical Informatics [25], Journal of Rehabilitation Medicine [27], and American Journal of Tropical Medicine and Hygiene [1].

Why Write a Systematic Review?

Unlike a literature review for a report or early research, a systematic review looks carefully at a body of literature based on a highly specific question. It is "a comprehensive, transparent, and systematic literature review method for preparing, maintaining, and disseminating high-quality evidence" [28]. Systematic reviews can be used in any industry, but they are most often seen in the medical field, and they often comprise effectiveness questions of specific interventions [28]. A systematic review can be qualitative or quantitative in nature, and it can extend into a meta-analysis with some additional data extraction during the analysis phase. A systematic review uses "explicit, systematic methods that are selected to minimize bias, thus providing reliable findings from which conclusions can be drawn and decisions made" [29]. It reports its findings using an industry-accepted reporting mechanism such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [29,30]. In addition, it examines a range of literature and filters as well as analyzes and summarizes the data into a condensed set of results and conclusions (Figure 1) [31].

Figure 1. Levels of evidence analyzed in a systematic review.



Methods

Integrating a Systematic Review Into an Academic Course

Much of the timing and order of steps in this process revolve around a semester course in the Master of Health Administration program at Texas State University [32]. I integrate my process into the course that aligns with my primary area of research, The Management of Health Information Systems. I use the systematic review as the major deliverable for that course. I start the process on the first day of class because the process is already being compressed from a 12-month timeline recommended by the National Institute of Health [29]. A traditional semester compresses the process into four months, and a compressed semester fits it into only 5 weeks: This is a brutal schedule, but possible with careful guidance. Students must manage readings from the primary text for the course and those inherent to their review. Every class comprises 50%-60% text material and the remainder systematic review. During the systematic review portion of the course, the author provides about 15-20 minutes of instruction for the next step in the process. This instruction is reinforced on the image map with similar instructions previously recorded (Multimedia Appendix 1).

Texas State University has many resources available that the author requires for the systematic review. The LMS enables collaboration and document sharing. The library provides access to a variety of health-related databases such as PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and CENTRAL (Cochrane Central Register of Controlled Trials). Students and faculty have access to Journal Citation Reports (JCR) and Cabell's database. They also have access to RefWorks, Zoom, and Office 365. Regardless of

student preferences, I require the use of university resources. Some groups prefer to use a service like Google Docs, but from my experience, students change access to these services between semesters, which hinders further refinement of the work later. The LMS serves as the document repository in case the author chooses to rewrite, expand, or build upon the review later as a coauthor or to invite other subject-matter experts to contribute. It is also ensures the group is maintaining proper workload and not procrastinating. I can also determine from the products uploaded if there are issues of communication difficulties or negative group dynamics and I can provide additional guidance to the group or to the class when it seems like the research is headed in the wrong direction. I also rewrite sections when the group submits them in a timely manner without penalty of grade, to incentivize timely submissions.

Form Groups, Choose a Topic, Read on That Topic, Develop a Research Question

After introduction of the syllabus for the course, the author unveils and orients the students to the process map (Multimedia Appendix 1). Students self-form into groups of 3 or 4. Ideally, the group needs to have at least three people to enable a tie-breaker opinion [29]. Groups larger than four people tend to invite social loafers, which complicates group dynamics. I do not join immediately as a coresearcher because when I do, I tend to take over the project: This action does not enable the students to learn. I teach, mentor, and guide the students through the process throughout the semester. I help them overcome barriers; guide them through tough spots; and at times, mediate between group dynamics. I also use authorship guidelines from the International Committee of Medical Journal Editors (ICMJE) guidelines [33]:

- Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work;
- Drafting the work or revising it critically for important intellectual content;
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

After the students self-form into groups, they sit in their groups for the remainder of the term. They also determine the roles for their team members: leader/project manager (to manage workload, set milestones and deadlines, and ensure regular group meetings using Zoom if necessary); editor (to work with RefWorks and write the review in one voice); literature matrix manager (to create and maintain the literature matrix in Excel); and for those groups with four members, a graphic artist (to create figures, tables, and other graphics in proper formats). I instruct the project manager to ensure documents integral to the review are uploaded to the LMS weekly. I also provide a set of deliverables and due dates to help them manage their time effectively. For instance, the literature matrix is an Excel document with several iterative tabs: Google Scholar search, abstract screening with Kappa, article analysis, themes, additional analysis, and charts.

Students conduct a basic search on their topic in Google Scholar. Google Scholar is not a research database, and its filter mechanisms are rudimentary. However, it serves as a good starting point for general research because it combines published research with grey literature. Students sort the results by date and every member of the group reads the top 10 articles; by the following class, they answer the following questions: What is my topic? What research has already been conducted on it? What research has not been conducted? The traditional-semester course meets once per week; therefore, the goal by the following week is for all members of the team to understand the topic. They identify 2-3 possible areas that have not been addressed through published research and could serve as their own research question. These 10 articles form the Introduction section of the systematic review, which includes the background, rationale, and objective(s) of the review, per the PRISMA checklist [30]. The literature matrix manager starts with a blank workbook and names several tabs that represent the major steps of the process. The Google Scholar tab of the literature matrix contains the following fields: date of publication, authors, study title, journal, impact factor, study design, key terms, technology intervention, results, observations from each group member, and a recommendation from each group member of whether to keep or reject each article in the analysis. These articles become the first 10 references.

Journal Selection, Journal Formats, and Established Principles of Scientific Writing

I highly consult the JCR as a source of quality metrics for journals and ask students to enter this information into the literature matrix. Based on the entries in the literature matrix, students observe the journals already publishing on their topic, which are the journals most likely to publish on their topic again. I ask project managers to write to the editors of the top three journals publishing on their topic. An example of verbiage for this email is provided on the image map. Journal editors may send only a form response that they cannot opine on a topic without sending the article for peer review: This is not a “no.”

In the second-class meeting, students provide an article critique of an article already published from the course (links to all articles published in the course are included in a folder in the LMS and link through the university library to meet copyright requirements). The critique is focused on how closely the published article followed the PRISMA checklist. The purpose of this deliverable is to alleviate fears about this onerous project and to show the level of formatting that the journal’s typesetting process provides. The process map itself is intimidating (a repeated comment on the course critiques). The longer students procrastinate starting the systematic review, the lower the quality of the review and the lower the likelihood that it will be of sufficient quality for publication. The article critique shows the students that the process itself is systematic in its approach, but it is not insurmountable, and complex formatting is not required at the authors’ level. The critique illustrates that journals dictate the preferred writing style. The published articles do not completely adhere to every step of PRISMA, but they include most of them. The peer-review process often strips out entire subsections of the PRISMA checklist. Many subsections of PRISMA are combined to enable better flow of the manuscript.

At the end of the critique, I ask students to follow PRISMA as closely as possible. If any portion of PRISMA does not apply to the reviews, they will at least address each step and state why it does not apply. By the end of the first week, students have created a preliminary literature matrix that documents details about and observations from the first 10 articles. The literature matrix lists and rank orders the top three journals most likely to publish their review. Students transcribe this information in a PowerPoint presentation titled "Author's Guidelines" (Textbox 1). As depicted by the figure, the first line is a link to the journal's page that provides all details of the guidelines. At the end of the semester, the author grades the format of what students write based on the Author's Guidelines from the preferred journal.

As depicted by the image map in Multimedia Appendix 1, 12 articles published by the Journal of Clinical Epidemiology in 2013 are integrated into the process [35-46]. These articles walk readers through getting started, [35] title and summary [36], introduction [37], methods [38], results [39], discussion [40], references [41], authorship [42], selecting a journal [43], submitting the article [44], responding to reviewers [45], and tables and illustrations [46]. They are excellent articles that I teach from regularly. Many portions of my image map in Multimedia Appendix 1 were inspired by these articles. Due to the compressed schedule already dictated by an academic semester, students do not submit the article themselves or respond to reviewers as part of the assignment. If I enter into a coauthorship agreement with students, I serve as the corresponding author and handle all rewrites. I teach the students about these important steps in class, and after the course has ended, I keep them all informed of the article's progress through the publication process, per ICMJE.

Textbox 1. Author's guidelines: a deliverable for early class period.

Choice 1: Applied Clinical Informatics

- Author's guidelines [34]
- Writing style: Vancouver
- Length limit: 2500-3000 words, not exceeding 5000 words
- Impact factor: 1.306 (2018)
- Listed in Journal Citation Reports or Cabell's database: yes
- Acceptance rate: <50%
- Time to publish: unknown
- Open access fee for publication: US $2400

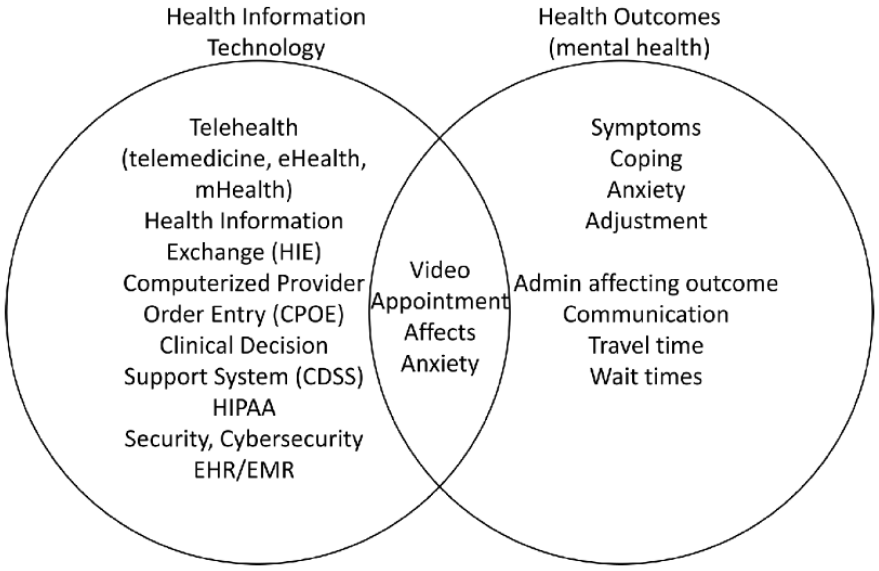
Introduction Section and the Importance of a Specific Objective Statement

The introduction section comprises a definition of major concepts and how they are related: This can be visualized in a Venn diagram (Figure 2). The first big concept is one application within health information technology, such as telemedicine or health information exchange (because that is the purpose of the course in which this deliverable is integrated). These definitions can come from the World Health Organization. The second big concept is one aspect of effectiveness and health outcomes such as reduced anxiety, improved patient-to-provider communication, increased adherence to treatment, fewer barriers to keeping an appointment, etc.

These definitions come from the professional organizations that care for the specific condition under study such as mental health, cardiovascular health, or prenatal care. The introduction defines these concepts and where they intersect. The introduction should list the research that has been conducted on this intersection so far, and it should culminate in what has not been studied (or needs to be studied further) [37]. This should be logically followed by the objective statement.

The objective statement is a specific point in the intersection of the important concepts. It clearly defines what the researchers intend to investigate. The objective statement should include all aspects of PICO (population, intervention, comparison, and outcomes) that are included on the second tab of the literature matrix as part of the analysis [29]. The importance of a clearly defined objective statement cannot be understated. This objective statement serves as a litmus test for group members to determine whether an article appeals to their purpose. Many articles are not properly indexed, and therefore, many are not germane to the research that students are trying to conduct. When students struggle to agree on articles to include in their analysis, I continually refer to the objective statement that they have written and agreed upon in the introduction section. I also help groups rewrite this section prior to moving onto the database searches.

Figure 2. Venn diagram showing the intersection of major concepts where research is to be conducted.



The Database Search, Abstract Screening, and Cohen Kappa

Referring to the literature matrix, students should have collected the key terms from the initial 10 articles from the introduction. These terms and Boolean operators serve as the starting point for what will be used to search the research databases. Beginning with these search terms, students refer to PubMed's Medical Subject Headings (MeSH), because it lays out the hierarchy of index terms under which it classifies articles. When a student types in "health information technology," for instance, some useful information is portrayed. This exact term is not indexed in PubMed, and therefore, a search that includes this key term would not be productive. However, changing the term to "health information management" yields richer results (Textbox 2). Under "entry terms," the MeSH hierarchy shows that several similar terms would yield the same result, such as health information management, and that there are several parent terms to the one entered. There is one additional term listed below health information management.

A basic understanding of how MeSH indexes articles makes the search string more effective at identifying articles appropriate for analysis. If a student clicks on the last term, "health information exchange" additional information is portrayed. If a student group wanted to analyze the effect of health information exchange on readmission rates to emergency rooms, they would know that similar terms such as "medical information exchange" would already be included, which simplifies an exhaustive search string. I encourage students to experiment with several combinations of their search terms to familiarize themselves with MeSH and ensure their search string is exhaustive in PubMed.

Students filter their results below 100 results using filters such as the last 10 years; omit other reviews; and if necessary, only include those in full text. The same search string is used in at least one other database. I recommend CINAHL and CENTRAL, and in those databases, remove MEDLINE, which takes care of most of the duplication with PubMed. When both CINAHL and CENTRAL are used, there is a great deal of overlap, which complicates the removal of duplicates. This is particularly problematic when there are several hundred articles to organize. Students download results from all databases to a csv file, rearrange columns so that they match, and then combine all results into one worksheet in the literature matrix to enable analysis. Students remove duplicates and screen abstracts for appropriateness to their objective statement. Students also download abstracts to a simple text file, matching the numbers to the literature matrix. This makes it easy for group members to screen abstracts. The project manager divides workload on the literature matrix with Xs next to the article entry, so that two group members review each abstract and opine on its appropriateness. This technique is supported by the Assessment Methodology Quality of Multiple Systematic Reviews (AMSTAR) [47]. An example of the workload allocation is provided in the image map (Table 1). The author asks the literature matrix manager to add a column for him, so that he can randomly screen articles on his own as part of the process. This enables him to render assistance when the group has difficulty reaching agreement.

Textbox 2. Medical Subject Headings term search result.

Entry terms:

- Health Information Managements
- Information Management, Health
- Information Managements, Health
- Management, Health Information
- Managements, Health Information All MeSH Categories
- Information Science Category
- Information Science Information Management Health Information Management Health Information Exchange

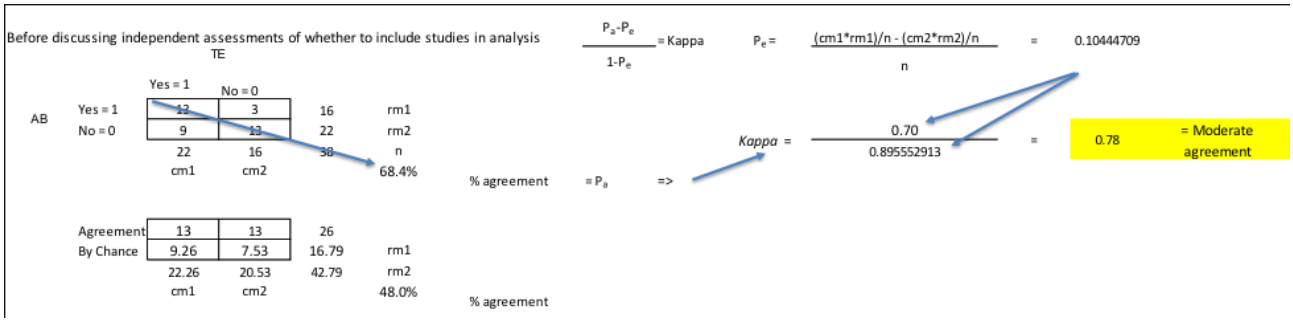
Table 1. Division of workload. "X" indicates which article is being reviewed.

	Student Reviewer 1	Student Reviewer 2	Student Reviewer 3	Author	Final decision
Article 1	X	X			
Article 2	X	X		X	
Article 3	X	X			
Article 4		X	X	X	
Article 5		X	X		
Article 6		X	X	X	
Article 7	X		X		
Article 8	X		X	X	
Article 9	X		X		

The editor of the group should write a statement of qualification from the objective by which students can screen their abstracts; for example, articles qualify for analysis in the systematic review if they analyzed cardiovascular health using one or more interventions of telehealth or document health medical outcomes and were published in the last 10 years. Over the next week, between class meetings, students in the group will screen abstracts to determine if they are germane to their objective and replace the "X" of workload assignment with a "1" or "0," indicating keep or reject. By the end of the screening process, students typically end up with a group for analysis between 30-60 assignments. This is a good point to register the review with a service like PROSPERO (International Prospective Register of Systematic Reviews), because it is far enough along to have a firm objective statement, but it is prior to analysis being performed. Prior to the next class session, the project manager holds the first "consensus meeting" in which the group discusses disagreements and makes a final determination on the group of articles for analysis. Discord is alleviated by a third member reading the abstract. Based on the group's recommendations, the PRISMA flow diagram can be started. Based on the 1s and 0s in the literature matrix, I calculate the Cohen kappa statistic using a series of Chi-square tables (Figure 3 and Multimedia Appendix 2) [48,49].

The literature matrix manager creates a third tab in the workbook with the final group for analysis and pastes those articles chosen for analysis from the previous tab. The project manager allocates workload, ensuring each article is analyzed by two reviewers in the same manner as the screening of abstracts. I ask the literature matrix manager to include a column for him as well to provide additional analysis. The literature matrix serves as the data extraction tool. The fields in the worksheet are database, date of publication, journal, authors, title, population, technological intervention, study type, comparison/control, outcomes, sample size, bias within study, effect size, country of origin, and anything else of relevance to the objective. Reviewers should also scan the references to identify articles missed by our search. External to workload assignments, I randomly choose articles in the list and provide my own observations. This variety of fields enables a thorough analysis of the articles in the review and the identification of common themes throughout the articles. It provides enough data to present visually through charts and enables a meta-analysis later.

Figure 3. Calculation of kappa statistic using a series of Chi-square tables.



This is the longest phase in the process (approximately 3 weeks), and it includes at least two additional consensus meetings. The second consensus meeting should enable group members to discuss what they have found so far, identify any additional articles from references that the database search missed, and discuss potential themes (common threads through articles). This step occurs only 2-3 weeks after the start of the course, so realistically, students are still figuring out their topic and how to conduct a systematic review. I realize this reality and provide regular coaching and class exercises to keep the students on task. Students will read all articles assigned to them while collecting data. I suggest the students read each article a second time after the first consensus meeting to identify additional themes that occur between articles. Themes will not surface until several articles have been read and analyzed. It takes multiple reads to thoroughly digest the group of articles. The third consensus meeting should identify the final set of themes and group the observations into these themes; for example, cost savings and additional expenditures are both "cost" and improved mobility and increased range of motion are both "improved health outcomes." Grouping into themes simplifies data summary and additional analysis.

Results

The literature matrix contains all the data extracted from the articles, and as such, it serves as the source for tables, charts, etc. Typically, the first table included in the review provides the observations and themes identified in the articles. Another table contains PICO and observed bias (I recommend this serve as an appendix for journals that do not offer tables in landscape view). An affinity matrix can be created to identify themes throughout the group for analysis, countries of origin, outcomes reported, and anything else of significance. As a rule, I recommend the results section be terse but informative. A table should be included that lists the articles organized by date, newest to oldest, with a brief sentence of the analysis performed pertinent to the objective statement. The sentence that introduces the table should list all the articles as references. This is important because many journals must have a requirement to list the article outside of a table, and by listing them in order by date, this order is now set for discussion. As previously mentioned, a more extensive table organized by PICO should be included as an appendix. Discussion and interpretation of the results should be reserved for the Discussion section.

Discussion

Overview

This protocol was designed to help graduate students publish a systematic review in a high-quality, peer-reviewed journal. How the protocol addresses each section has been detailed and examples have been provided. This protocol has been proven with a history of successfully published articles over time, but end products are only as good as the level of effort invested into the analysis of articles.

The PRISMA checklist identifies several subsections for the Discussion section: Summary of evidence (which is where analysis of results takes place), limitations (and bias), and conclusions (with interpretation of results) [30]. The Discussion section is also the place for suggesting future research and comparison to previous research. The final section in the PRISMA checklist is the funding paragraph. Each journal has specific wording for this paragraph that can be found in the Guidelines for Authors.

Helping Graduate Students Publish

At the end of each term, I grade work based on process, format, and substance. I do not grade harshly because I do not expect students to be proficient in writing for publication at the master's level. After entering grades for the work the students have done, I assess each article for its potential to be published. As in any program, not all groups take the assignment seriously. This seems to occur about 25% of the time. These groups follow the process and generally do what they were asked, but often, their analysis is shallow. Occasionally, a group omits a key term that radically changes the search results and group for analysis. Depending on the workload, I prioritize the articles from most to least potential and enter into a coauthorship agreement with the students. I spend my semester breaks duplicating the search results, analyzing all articles, and discerning meaning. I fine-tune graphics and ensure all formatting meets the requirements of journals. I then carefully comb through each section, strengthening the conclusions. I ensure the standard of the product meets those set by the editor. My level of effort to rewrite the product determines where I put my name on the authorship line. I send out the final version of the manuscript to the students prior to submitting to a journal. I obtain permission from the school Chair to fund the article using Open Access and then submit the article and track its progress. Some articles take years to matriculate through the publication process [11]. Others take only a couple months [26].

Continual Improvement to the Process Map

I continue to make small modifications to the process where needed, but it has remained in its current state now for about 2 years. Due to its static nature, it was the right time to share what I have used. At the university in which I teach, I created an LMS project site with the image map and all related resources. This can be imported into other courses and appears as a navigation button. So far, only two other professors have used it in this manner, but it is available for others upon request (access must be granted to the site).

Limitations

There are many limitations to conducting systematic reviews, but this protocol addresses and overcomes many of them. Selection bias is addressed through exhaustive searches with MeSH terms, using the same search string in multiple databases and by using multiple reviewers. This is supported by AMSTAR [47]. Publication bias is addressed by including grey literature in the search.

Conclusions

I have found success with this method, and peers have asked me to write this article as both an aide for students and other professors who want to use the image map in their teaching. So far, this method has helped 77/151 (51%) graduate students publish with iterations of this protocol. Two manuscripts are in press, one is under consideration on its second peer review, two manuscripts are under consideration on their initial peer review, and three are in progress. I wish success to others who might use this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
HTML5 image map that provides instructions to augment teaching in classroom. URL to dynamic code; https://h5p.org/h5p/embed/28817.
[PNG File , 192 KB - resprot_v8i10e15490_app1.png]

Multimedia Appendix 2
Literature matrix Excel worksheet, second tab, and "abstract screening", from which a kappa statistic is calculated.
[XLSX File (Microsoft Excel File), 39 KB - resprot_v8i10e15490_app2.xlsx]

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Abbreviations

AMSTAR: Assessment of Methodological Quality of Multiple Systematic Reviews
CENTRAL: Cochrane Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
ICMJE: International Committee of Medical Journal Editors
JCR: Journal Citation Reports
LMS: Learning Management System
MeSH: PubMed Medical Subject Headings
PICO: population, intervention, comparison, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews

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