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Protocol

Using Mobile Technology (pMOTAR) to Assess Reactogenicity: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Accurate safety monitoring in HIV vaccine trials is vital to eventual licensure and consequent uptake of products. Current practice in preventive vaccine trials, under the HIV Vaccine Trials Network (HVTN), is to capture related side effects in a hardcopy tool. The reconciliation of this tool, 2 weeks after vaccination at the safety visit, is time consuming, laborious, and fraught with error. Unstructured Supplementary Service Data (USSD), commonly used to purchase airtime, has been suggested for collection of safety data in vaccine trials. With saturated access to mobile phones in South Africa, this cheap, accessible tool may improve accuracy and completeness of collected data and prove feasible and acceptable over the hardcopy tool.

Objective: The objective of our study is to develop and implement a USSD tool for real-time safety data collection that is feasible and acceptable to participants and staff, allowing for a comparison with the hardcopy tool in terms of completeness and accuracy.

Methods: This feasibility study is being conducted at a single study site, the Centre for the AIDS Programme of Research in South Africa eThekwini Clinical Research site, in South Africa. The feasibility study is nested within a parent phase 1/2a preventive HIV vaccine trial (HVTN 108) as an open-label, randomized controlled trial, open to all consenting parent trial participants. Participants are randomly assigned in a 1:1 ratio to the hardcopy or USSD tool, with data collection targeted to the third and fourth injection time points in the parent trial. Online feasibility and acceptability surveys will be completed by staff and participants at the safety visit. We will itemize and compare error rates between the hardcopy tool and the USSD printout and associated source documentation. We hypothesize that the USSD tool will be shown to be feasible and acceptable to staff and participants and to have superior quality and completion rates to the hardcopy tool.

Results: The study has received regulatory approval. We have designed and developed the USSD tool to include all the data fields required for reactogenicity reporting. Online feasibility and accessibility surveys in both English and isiZulu have been successfully installed on a tablet. Data collection is complete, but analysis is pending.

Conclusions: Several HIV preventive vaccine trials are active in Southern Africa, making tools to improve efficiencies and minimize error necessary. Our results will help to determine whether the USSD tool can be used in future vaccine studies and can eventually be rolled out.

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KEYWORDS

research protocol; mobile health application; HIV preventive vaccines; telemedicine; mobile applications; AIDS vaccines

Introduction

Rationale

Despite the gains made in the provision of antiretroviral treatment and, more recently, prevention globally, in 2015 there were 1.8 million new infections worldwide. South Africa has the biggest antiretroviral treatment program in the world, with approximately 3.4 million people being treated [1]. In November 2015, South Africa registered emtricitabine/tenofovir disoproxil fumarate (Truvada) for preexposure prophylaxis in key populations yet, in 2016 alone, approximately 270,000 incident infections occurred [2]. A safe, effective HIV vaccine is still seen as the solution to epidemic control and, ultimately, elimination.

Safety monitoring in HIV vaccine clinical trials is vital, from early-phase safety and immunogenicity testing, to late-phase efficacy testing and eventual licensure of candidate vaccines. An essential part of safety monitoring is the collection of side effects data reported by participants after they have received a study product and for 3 to 7 days after leaving the clinic. All preventive HIV vaccine trials collect reactogenicity data: this is a set of known and expected injection site and systemic symptoms and signs that are related to the vaccine. Unexpected side effects (classified as adverse events) are also collected on study-specific case report forms (CRFs). The duration of the reactogenicity period depends on the protocol, and adverse event data collection periods are defined per protocol, depending on the seriousness of the event. In sub–Saharan Africa, a suite of trials in response to the modest results of the RV144 trial [3] has been launched to progress a modified HIV clade C–specific vaccine candidate to licensure and to deepen the understanding of the mechanisms of immune protection against HIV. Concurrently, several early-phase HIV vaccine trials, 2 efficacy trials, and a proof-of-concept neutralizing antibody infusion trial are being conducted. The possibility of increased occurrence of safety events is thus greater in these populations and simultaneously demands more accurate, efficient methods of data collection.

Vaccine Uptake and Efficacy

Public perception and tolerance of licensed vaccine risk indicates that, in the absence of a direct threat from disease, some people will not undergo vaccination unless absolute safety can be assured [4]. If a successful HIV vaccine candidate is licensed in the future, there is a risk that people may avoid vaccination due to safety concerns. A systematic review of barriers to participating in an HIV vaccine trial analyzed common themes between studies and found that vaccine side effects and safety were noted as barriers to participation [5]. The collection of accurate safety data is vital to address these concerns. In a systematic review of 50 randomized controlled vaccine trials in developing countries, consistent documentation was key to the successful implementation of international safety standards in resource-poor settings [6]. Modern technologies, including short message service (SMS) and mobile phone apps, were recommended as possibly facilitating the monitoring of vaccine safety in remote areas, where access to internet connectivity may not always be possible [6]. This technology would allow for real-time data collection, offering an improvement over the hardcopy tool. Standardization of safety reporting across multiple sites in developing countries was borne out in a systematic review of safety data reporting in vaccine trials for malaria, tuberculosis, and HIV, which focused partly on methods used to collect and report side effects [7]. This review noted imprecision and inconsistency of body temperature reporting, which is a key objective safety parameter. The proper collection and documentation of unexpected side effects also allows for regulators and sponsors alike to link uncommon side effects across trials and sites, enabling the identification of sporadic, serious side effects [7].

The Hardcopy Tool

Research staff collect reactogenicity data initially at the study site before and up to 60 minutes after vaccination on CRFs. For the remainder of the reporting period, participants collect data off-site on a hardcopy tool. This demands extensive, intensive training of participants on completion of this tool (in the language of their choice) and training on the use of a thermometer and ruler, for temperature and injection site reactogenicity assessments, respectively. Participants are also taught to objectively grade the severity of symptoms using a standardized set of symptom criteria. Research staff are directed to contact participants by telephone daily (in early-phase protocols) or after 3 or 7 days (for later-phase protocols) to check on participants' health, collect and objectively grade symptoms, and provide refresher training as needed. Objective grading determines whether a symptom is mild, moderate, severe, or life-threatening and facilitates clinical decision making and symptom management on continuation of vaccinations per participant and protocolwide. Staff document these data directly onto corresponding CRFs on working days and in a site-developed document outside of clinic operational hours. This is then transcribed to CRFs on the next working day. At the 2-week postvaccination safety visit, research staff review the CRFs, hardcopy tool, and site-developed source document (if applicable) with each participant to ensure that CRF data are accurate. This process is repeated for each vaccination visit within the protocol.

This exercise remains fraught with error from a multitude of sources: daily data collection is not directly attributable to participants, and there is no evidence that data are completed contemporaneously; participants are often uncontactable at the agreed-upon time or do not have the hardcopy tool with them when contacted by staff to complete CRFs; participants may not return the hardcopy tool to the site at the safety visit or at all, and data have to be reconstructed based on participant recall 2 weeks later; participants tend to grade symptoms subjectively despite training; many hardcopy tool entries are incomplete or incorrect; and staff need to document each error in detail between the relevant documentation, making the time and labor the task consumes proportional to the number of errors. In

addition, national research regulators may consider all or part of the hardcopy tool as a source document, and errors such as incorrect dates, overwriting, and entry of redundant or unclear information by the participant must be documented in explicit detail. If not, the site risks incurring serious findings by external monitors, directly affecting protocol quality metrics. For moderate reactogenicity and other adverse events, the site relies on participant-initiated contact to determine whether a clinic visit is required as mandated by the protocol. If this is missed, a protocol deviation must be reported to the sponsor, regulator, and ethics committee. More importantly, participant safety may be severely compromised if an unreported symptom fulfills a pause rule for the study, when all further vaccinations at all sites may be held, pending a risk assessment.

The alternative to the systems detailed above would be daily clinic visits for the duration of the reactogenicity period for each vaccination time point. This would increase the cost of participant reimbursements, negatively affect travel and convenience for participants, and increase the research site's workload for the day. The conduct of multiple studies per site, necessitating a process efficiency system to reduce visit duration, does not support this labor-intensive and inefficient process.

Mobile Health and Unstructured Supplementary Service Data

Mobile health (mHealth) is the practice of medicine and public health supported by mobile devices, which have the potential to facilitate alerts, reminders, and data collection, substantially reducing the burden on health care systems [8-11]. Unstructured Supplementary Service Data (USSD) is a tool that transfers messages directly over the mobile operator network, allowing for an exchange between mobile phones and a network app. It is accessed by user request, making use of short codes or text strings to trigger certain services and facilitate high-speed, interactive, session-based communication. The text string, up to 160 characters long, can be used to establish a new session or to continue an established session, with asterisk (*) and hash (#) codes signifying the beginning and end of the request, respectively. Most importantly, it is accessible on basic mobile phones. In Botswana, research recommendations in mHealth have alluded to the successful use of USSD by health care workers to retrieve treatment guidelines [12].

South Africa is highly ranked fifth in the world for mobile data usage [13,14], with more active subscriber identity module cards than people and 128% active mobile connections among the population [15]. By mid-2013, total mobile phone subscriptions were estimated at over 68 million [13]. USSD could prove useful to implement real-time reactogenicity data collection, having several advantages courtesy of its menu-based platform, namely, speed and responsivity, affordability, real-time entry and access, automation, user initiation, and simultaneous mass usage. It is affordable and accessible, with the total cost of a typical session depending on duration of the session (20 cents per 20 seconds; US $0.074 dollar = 100 cents or 1 R). It allows only "yes" or "no" responses, thus shortening the session length and improving affordability. SMS text messaging is managed manually, can cost up to 100 cents per message, and would need to be initiated by the provider. Responses submitted by USSD are automatically deleted on the device, complying with data confidentiality requirements of Good Clinical Practice and the US Food and Drug Administration's Code of Federal Regulations Part 11. One of the cornerstones of the South African National Department of Health's mHealth strategy [16] commits the government to providing an mHealth implementation plan to strengthen research and development.

In this study, we propose the collection of reactogenicity and adverse event data using a customized USSD tool, with the objectives of developing and implementing a basic mobile phone-based USSD tool for the collection of reactogenicity data, establishing feasibility and acceptability among research staff and participants, and determining whether the accuracy and completeness is superior to the hardcopy tool. Piloting this technology in the research setting in a developing country such as South Africa in an early-phase trial will allow for optimization of the system to facilitate collection of safety data across multiple sites, in late-phase, large-scale studies and eventual programmatic rollout.

The South African regulator follows *South African Good Clinical Practice Guidelines* [17], which confirms the compliance of USSD data collection as acceptable.

Methods

Study Design

This is an open-label, randomized controlled trial under the HIV Vaccine Trials Network (HVTN) nested in the parent HVTN 108 trial, a phase 1/2a clinical trial to evaluate the safety and immunogenicity of HIV clade C DNA, and of MF59- or AS01B-adjuvanted clade C Env protein in various combinations, in healthy, HIV-uninfected adult participants. The parent study has a series of 4 vaccination time points in a 6-month period: at months 0, 1, 3, and 6. The study will use 2 consecutive vaccination time points, namely months 3 and 6, to implement the USSD tool, with postvaccination feasibility and acceptability surveys at the 2-week postvaccination safety visits. At months 0 and 1, all participants complete the hardcopy tool for reactogenicity assessment. The intervention is a purpose-designed, study-specific USSD tool that collects all the protocol-mandated reactogenicity data collected by the hardcopy tool. At the time of initiating this paper, the USSD tool and electronic surveys had been developed and approved, and enrollment was ongoing.

Setting

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site (ECRS) was chosen as the sole site for this study.

Approvals

The parent and this study were approved by the University of Kwazulu-Natal's Biomedical Research Ethics Committee; in addition, the parent study was approved by the University of Kwazulu-Natal's Institutional Biosafety Committee, the South African Medicines Control Council, and the Department of Agriculture, Forestry and Fisheries. The South African National Clinical Trials Registry number for the parent study is

NCT02915016. This pilot trial did not meet the US Food and Drug Administration requirements for trial registration. We received further review and approvals for this study from the HVTN 108 protocol team, the HVTN Regulatory Affairs office, HVTN Initiatives Program's review board, and HVTN Scientific Governance Committee.

Statistical Considerations

Accrual

Up to 30 slots may be allocated to the CAPRISA ECRS for the parent study. Recruitment for this nested study will target enrolling all consenting, healthy, HIV-uninfected adult participants aged 18 to 40 years enrolled in the parent study at the CAPRISA ECRS in a 1:1 ratio to the hardcopy or USSD tool.

Sample Size Calculations

We estimated the power for detecting a reduction in error rates for the USSD relative to the hardcopy tool arm via simulation. We assumed that the total number of errors for a single participant at a single visit would follow a Poisson distribution whose mean we determined by the study arm the participant was assigned to and differs depending on whether the participant was randomly assigned to use the USSD or the hardcopy tool. Data were simulated assuming 2 possible error rates for the hardcopy group and 2 possible group sizes, and the error rate for the USSD group was varied over a small range of values. The simulated data were fit using a Poisson regression model consisting of an intercept and a term for the study group, and the coefficient of the study group was tested for equality with 0.

Study End Points

We will calculate error rates for both the USSD and hardcopy tool for completeness (defined as an entry that should have been completed, but was not) and for accuracy (the level of agreement between the data collected either by hardcopy tool or by USSD and the entries on the reactogenicity CRFs following a discussion with the participant to confirm final data; staff transcription errors and participant completion errors will also be taken into account). This will be expressed as errors per 100 pages completed.

Conditions Under Which Power is Computed

For means, the reported error count range for the hardcopy tool is 5 ("very good") to 26 ("very bad"). We used a calculated average (mean) error rate, likely lying in the range of 13 to 17, to compute power (Table 1).

For sample size, we used a maximum possible enrollment into this ancillary study of 30 participants, based on the expected slot allocation for HVTN 108, which would result in 15 participants assigned to each of the USSD and hardcopy arms. Since we are unlikely to achieve the maximum enrollment, we computed power for 2 levels of enrollment that reflect poor and good consent rates. The poor level assumes that a total of 20 participants consent to the ancillary study—an expected 10 per group—which is a 56% consent rate. The good level of enrollment assumes that 30 participants will consent—an 83% rate—and would give us an expected 15 participants per group.

Since the data consist of repeated measures from individual participants, they require modelling that accounts for the correlation between measurements from the same person, and one standard way is to use mixed-effects models. Count data require us to use the generalized linear mixed-effects model framework, and we will employ the negative binomial family (rather than the Poisson) for the extra flexibility it provides. Our model will contain at a minimum a fixed effect for the method of data collection (USSD or hardcopy tool) and a random effect for participant. When writing the statistical analysis plan, we may consider models containing additional fixed-effect terms (eg, for sex, visit number), as well as more complex random-effect structures, and we will incorporate terms as appropriate based on model fit criteria such as the Akaike information criterion. Inference on the difference between methods will be made by testing whether the estimate of the collection method parameter is significantly different from 0 at the .05 level.

Table 1. Power for differential sample size and error rates.

Mean errors per participant per visit			Power to detect difference in means between HCT[b] and USSD[c] groups (%)	
HCT	USSD	Reduction in error rate[a], n (%)	10 participants per group	15 participants per group
17	14	3 (18)	40	55
17	13	4 (24)	65	80
17	12	5 (29)	83	94
17	11	6 (35)	95	99
13	10	3 (23)	51	69
13	9	4 (31)	80	90
13	8	5 (38)	95	99

[a]Unstructured Supplementary Service Data vs hardcopy too.

[b]HCT: hardcopy tool.

[c]USSD: Unstructured Supplementary Service Data.

Discontinuation and Early Study Termination

The number and percentage of participants who discontinue vaccination and thus who terminate the nested study early will be tabulated by reason and intervention arm in the pilot study.

Data Management

For participants enrolled into the hardcopy tool arm, the tool, CRFs, and other study documentation are the source for the reactogenicity data over the 7-day postvaccination reporting period.

For those randomly assigned to the USSD arm, the tool database printouts, CRFs, and other study documentation are the source for reactogenicity data. All participants randomly assigned to the USSD arm will also receive a backup hardcopy tool in the event of system errors that cannot be overcome with site support; these will also be used as source, if applicable. The tool database printouts of reactogenicity reports are transcribed onto CRFs by research staff.

Tools

Unstructured Supplementary Service Data Tool Development

The tool has been designed through a collaborative effort between the service provider Channel Mobile (Cape Town, South Africa) in consultation with the investigators and the parent study HVTN Clinical Safety Specialist team. The tool name is pMOTAR (pilot study of Mobile Technology to Assess Reactogenicity) for ease of reference for participants and research staff.

The following design features facilitate data input and collection. (1) All the data elements are included in the hardcopy tool of the parent study. (2) As data are entered on the mobile phone, uploads to the database are immediate. (3) Participants can access the system multiple times in one day, to facilitate completion of incomplete sessions. (4) A “preserve state” enables participants to continue from the last active screen where they left off, if they were previously timed out or could not complete the session for any reason. (5) Only minimal responses are required for ease of use, for example, selection of a number corresponding to the symptom, followed by selection of a number corresponding to the objective grading. (6) Participant responses indicative of potential safety events, such as a “yes” response to any expected or unexpected symptoms followed by free text to denote the symptom, will also be available to staff through contemporaneous alerts from the system routed to designated staff mobile phone numbers. (7) Participants can choose between 2 languages: English and Zulu. (8) Risk of harm is minimal, as confidentiality is assured in that entered data cannot be saved to the handset or transferred to another handset, and are automatically deleted following submission; only research staff have access to the entered data in the tool database. (9) Reverse billing is applied, such that participants can log on to the system even if they have no airtime. At the end of the session, the cost of the session is charged to the research site. This ensures ease of access to and use of pMOTAR with no possibility of the participant running out of airtime during a session. (10) Automated SMS reminders are sent out at 08:00, 12:00, and 15:00 if the system is not accessed and the tool is not completed. (11) Double entries have not been disallowed so as to facilitate entry of updated measurements or missed entries from a previous day that have been captured on a hardcopy tool, perhaps because of connectivity issues on the day of measurement. Each entry will trigger an SMS text message to alert study staff, who can call the participant immediately to clarify the reason and document the same in a chart note, such that duplicate entries in the database can be explained and analyzed appropriately.

Unstructured Supplementary Service Data Tool Database

The following tool database features facilitate contemporaneous access of information by research staff. (1) Printouts from the tool database will serve as source documentation for completion of CRFs. (2) Real-time access to the tool database allows staff to review data in a timely manner and determine whether immediate action to assess a participant’s response is required to clarify an entry or to facilitate a site visit to assess safety. (3) Reports can be downloaded and printed, and usage can be tracked based on mobile phone number patterns from the tool database. (4) An audit trail and an automatic daily backup of the tool database is made to an external drive at 04:00. (5) Physical servers are hosted at a secure data center with failovers (switching to a redundant or standby computer server on the failure or abnormal termination of the current server) to the Amazon cloud (Amazon.com, Inc, Seattle, WA, USA) and Azure (Microsoft Corporation, Redmond, WA, USA).

Unstructured Supplementary Service Data Tool Specifics

The flow of the USSD app service for reactogenicity symptom assessment is as follows. First, a mobile user initiates the service by dialing the USSD string defined by the service provider Figures 1-4 show sample screen flow strings.

Second, the USSD app server receives the service request from the user and responds by sending the user a menu of options. (1) The first menu allows selection of the preferred language, either 1 for English or 2 for Zulu; the user responds by selecting option 1 or 2 and then presses <SEND>. If the incorrect option is selected, the user selects <CANCEL> and reselects. (2) The next screen includes a greeting and a request to enter a 4-digit unique identifying code provided by the research staff. (3) Once the code is entered, an invitation to capture the temperature is loaded, allowing the participant to enter a measurement to 1 decimal point. (4) After the participant selects <SEND>, an automated menu of numbered *local* symptoms and choice of responses is sent to the user. Local symptoms also reflect whether vaccinations are given in the right or left upper arm, or both. (5) If the participant selects either redness or swelling at the injection site, they will be prompted to enter measurements in centimeters, initially from top to bottom, and then from side to side. (6) If the participant responds by making a single selection of another symptom, this will trigger an automated response from the app, which sends out the selection of grading (minimal, some, or major) by the participant. (7) Once the participant selects <SEND>, they are returned to the original symptom selection screen to select any other symptoms that may be experienced. (8) If no other symptoms have been experienced, the participant selects <NEXT>, then the system

loads the selection of *systemic* symptoms for completion. (9) If the participant responds by making a single selection of a symptom, this will trigger an automated response from the app, which sends out the selection of grading (minimal, some, or major, which equates to minimal, moderate, and severe) by the participant. (10) Once the grading for the selected symptom is selected and the participant selects <SEND>, they will be taken back to the original systemic symptom selection screen.

Figure 1. The Sample Unstructured Supplementary Service Data Tool (string 1).

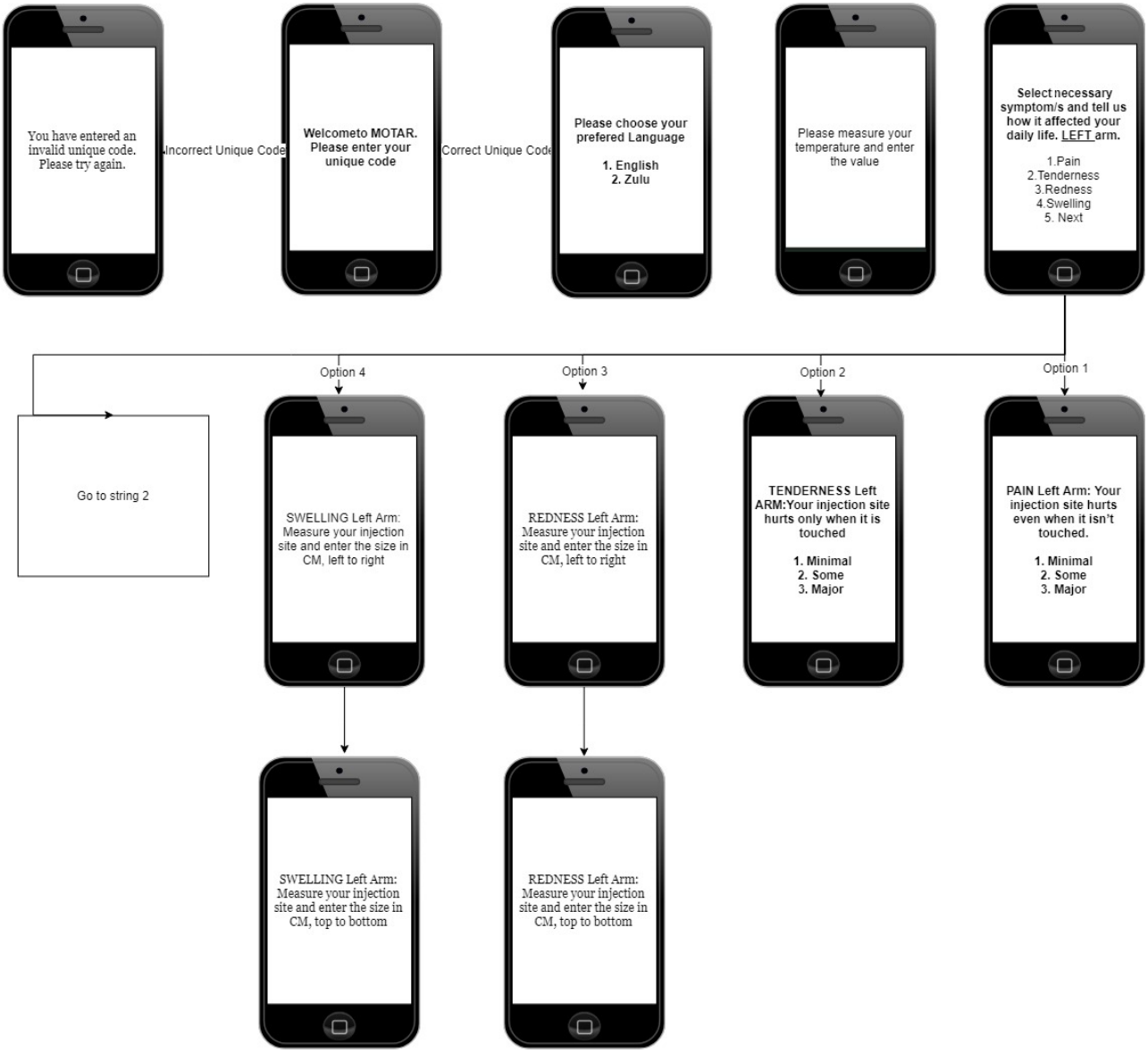
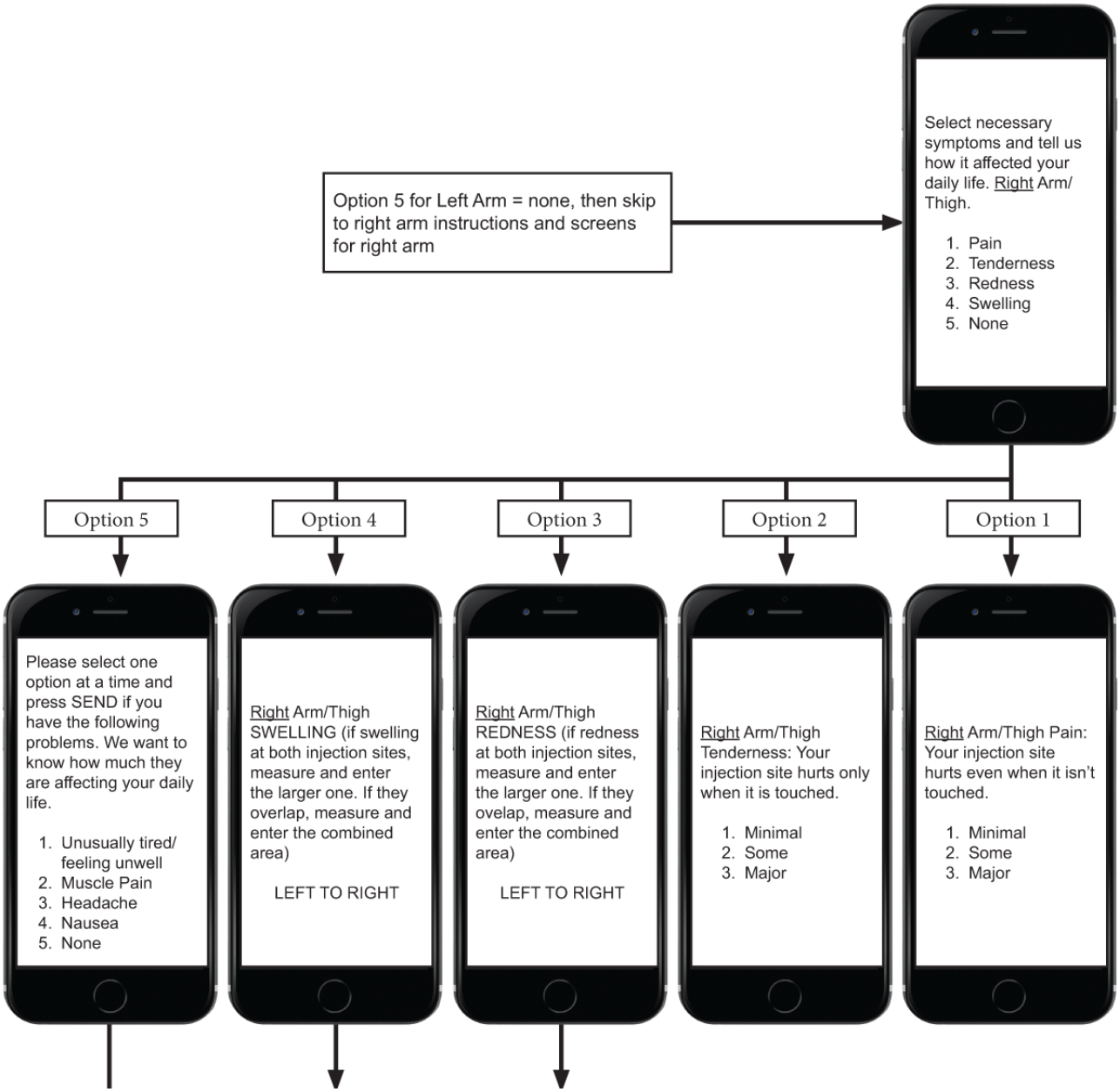


Figure 2. Part 1 of the Sample Unstructured Supplementary Service Data Tool (string 2).



(11) The last prompt from the system is for the occurrence of any other unexpected symptoms, not previously listed on any screens, and allows for free entry of text to describe the symptom. (12) Each response occurs in a matter of seconds, in quick succession, and in real time, and the participant is not able to skip any screens to get to the end.

Third, once a participant selects <SEND>, the entered data are automatically uploaded to the tool database and simultaneously deleted from the handset, ensuring confidentiality.

Fourth, the app automatically ends the session when <FINISH> is selected, then delivers a "Thank you" message to confirm completion of all questions to the participant.

Mobile phone numbers of consenting participants are obtained from the locator information of the parent study records and linked to unique confidential identifying 4-digit codes, which are assigned to the participant during training on the USSD program and used by the participant to access the app.

The Hardcopy Tool

The hardcopy tool (Figures 5-7) is provided by the research staff to the participant, who is trained in how to complete this tool on the day of vaccination, before leaving the clinic. If a participant experiences difficulty completing the tool at home, they are informed to contact the site for support or inform the staff during the daily call. Research staff telephone participants either daily or according to the protocol directive, with the expectation that the participant has access to the hardcopy tool at the time of the call. Research staff will ask the participant to share temperature and any local injection site lesion measurements with the research staff member, who then enters this information either directly onto the CRF on a working day or into a site-developed document for use on nonworking days off-site.

Figure 3. Part 2 of the Sample Unstructured Supplementary Service Data Tool (string 2).

pMOTAR Clinical Procedures

Informed Consent and Screening Procedures

Research staff obtain written informed consent in the preferred language of the participant and prior to any screening procedures.

Participants are screened at a visit prior to the third vaccination in the parent study vaccination series, followed by an assessment of eligibility, as per the inclusion and exclusion criteria. Selected information from the parent study, namely informed consent form and locator information, are accessed to confirm eligibility. The participant identifying number from the parent study is used to link data from this ancillary study to the parent study.

Enrollment and Randomization

Participants are enrolled and randomly assigned on the same day as the third vaccination, following a review and confirmation of eligibility, revisiting the informed consent form (as needed). Participants in the intervention arm are assigned a unique 4-digit code to access the USSD tool; participants in the control arm follow procedures for the parent study.

The randomization system uses computer-generated random numbers, so that if 30 participants are enrolled, there will be 15 in each arm. Sealed opaque randomization envelopes are provided to the study coordinator for storage, to be opened in sequential order. After the envelopes are opened, the date and time of opening the envelopes, as well as the research staff member's name, are documented on the envelope. This information is then noted on the randomization sheet.

Figure 4. Part 3 of the Sample Unstructured Supplementary Service Data Tool (string 2).

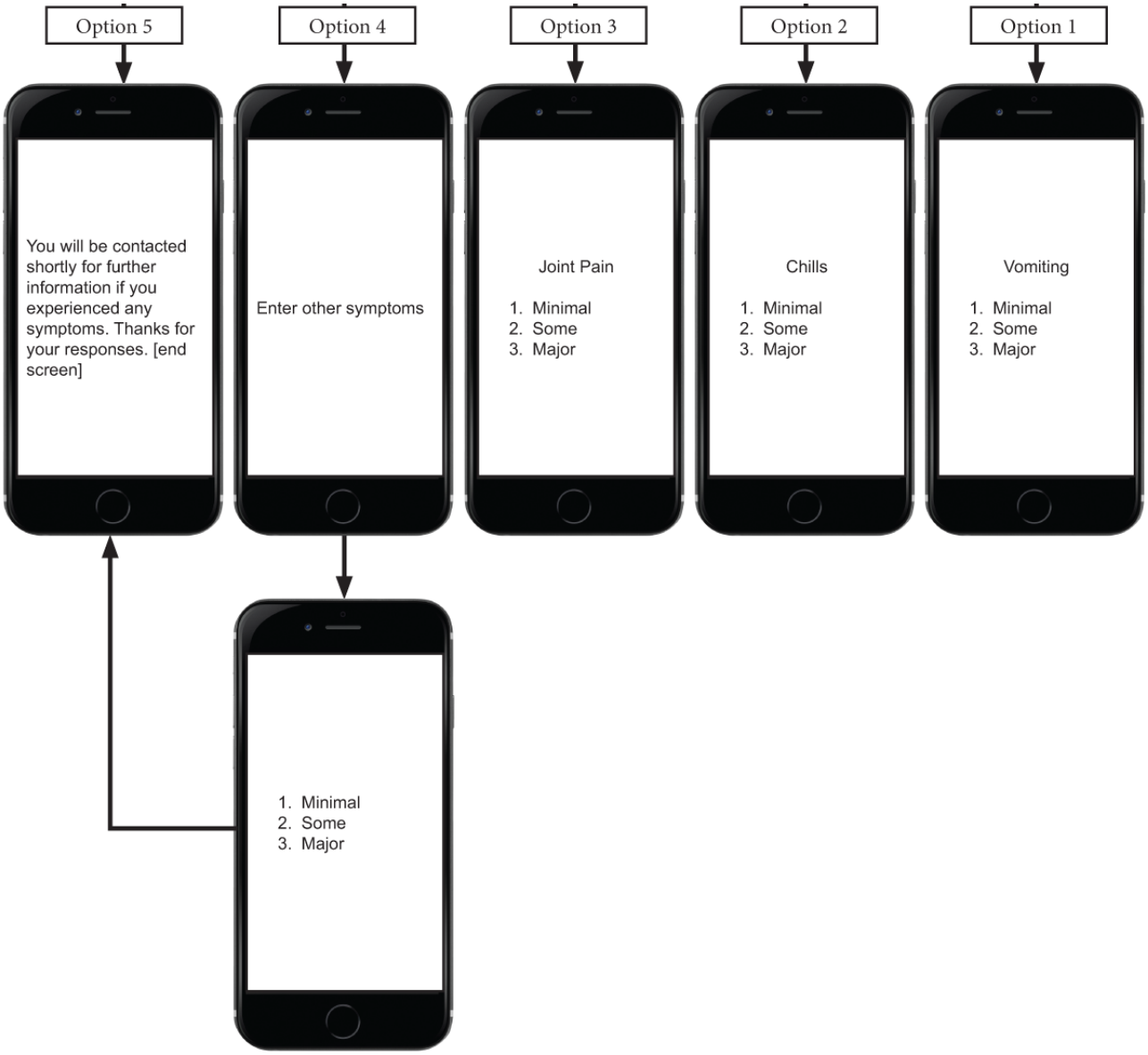


Figure 5. Sample hardcopy tool (page 1).

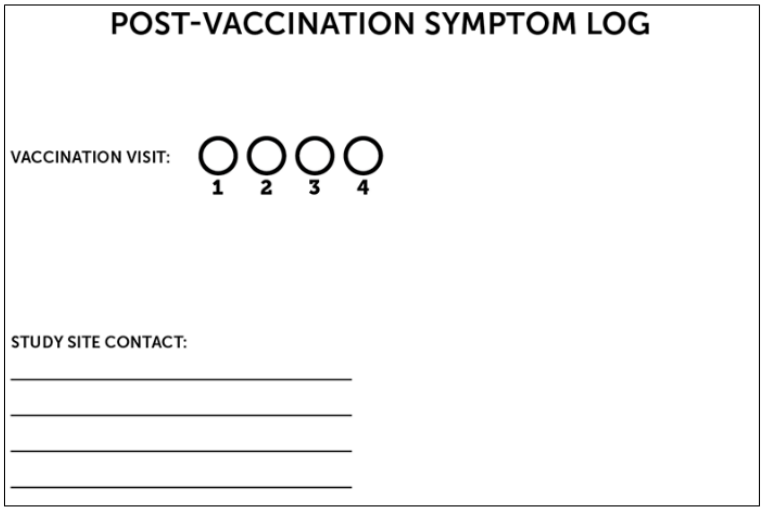
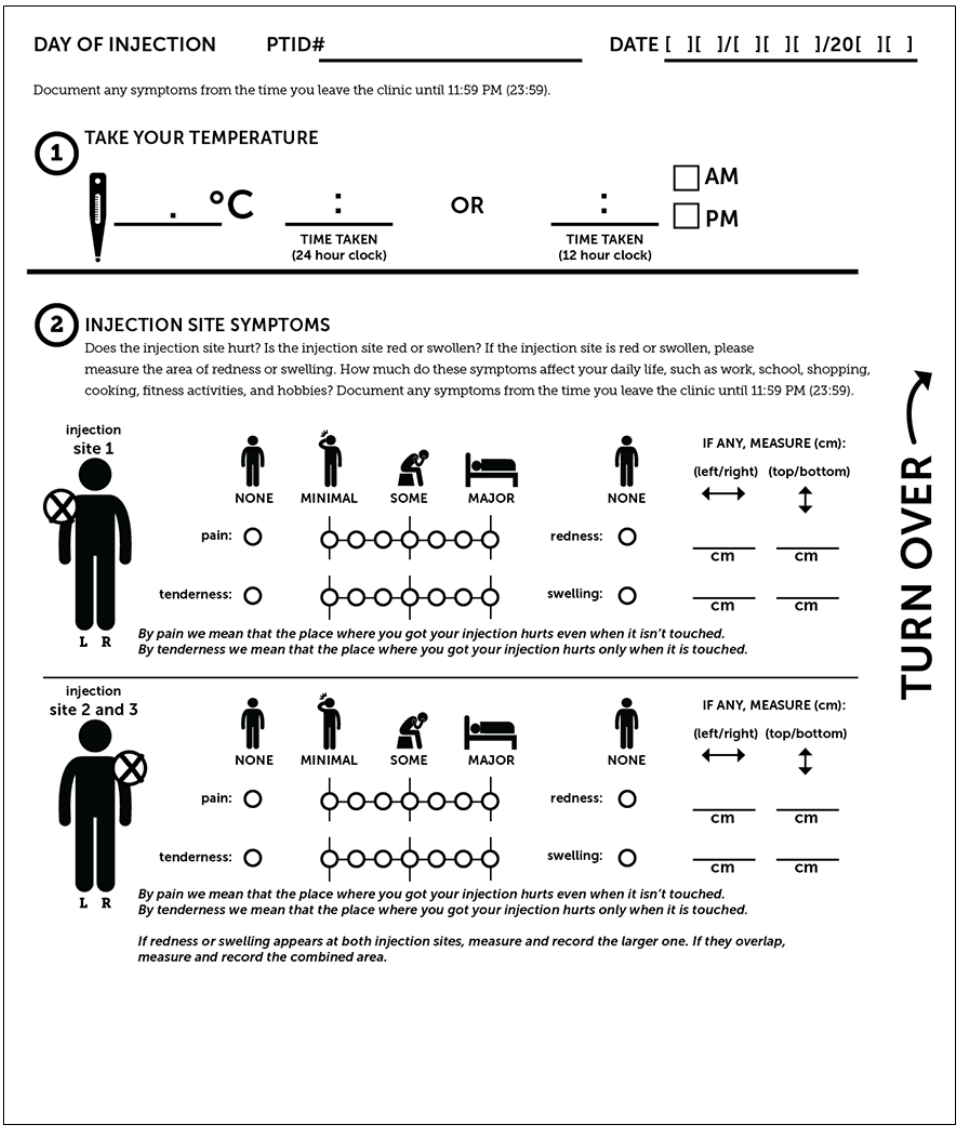


Figure 6. Sample hardcopy tool (page 2).



All participants are trained in the use of either the hardcopy or USSD tool, depending on arm assignment, and in the use of the thermometer and ruler. The participants in the intervention arm are trained in the use of the hardcopy tool as a backup; this training is repeated at the next vaccination time point (3 months after enrollment). Likewise, all participants, irrespective of arm

assignment, receive site contact details to assist with tool completion (if they experience difficulty once off-site) or to report additional problems.

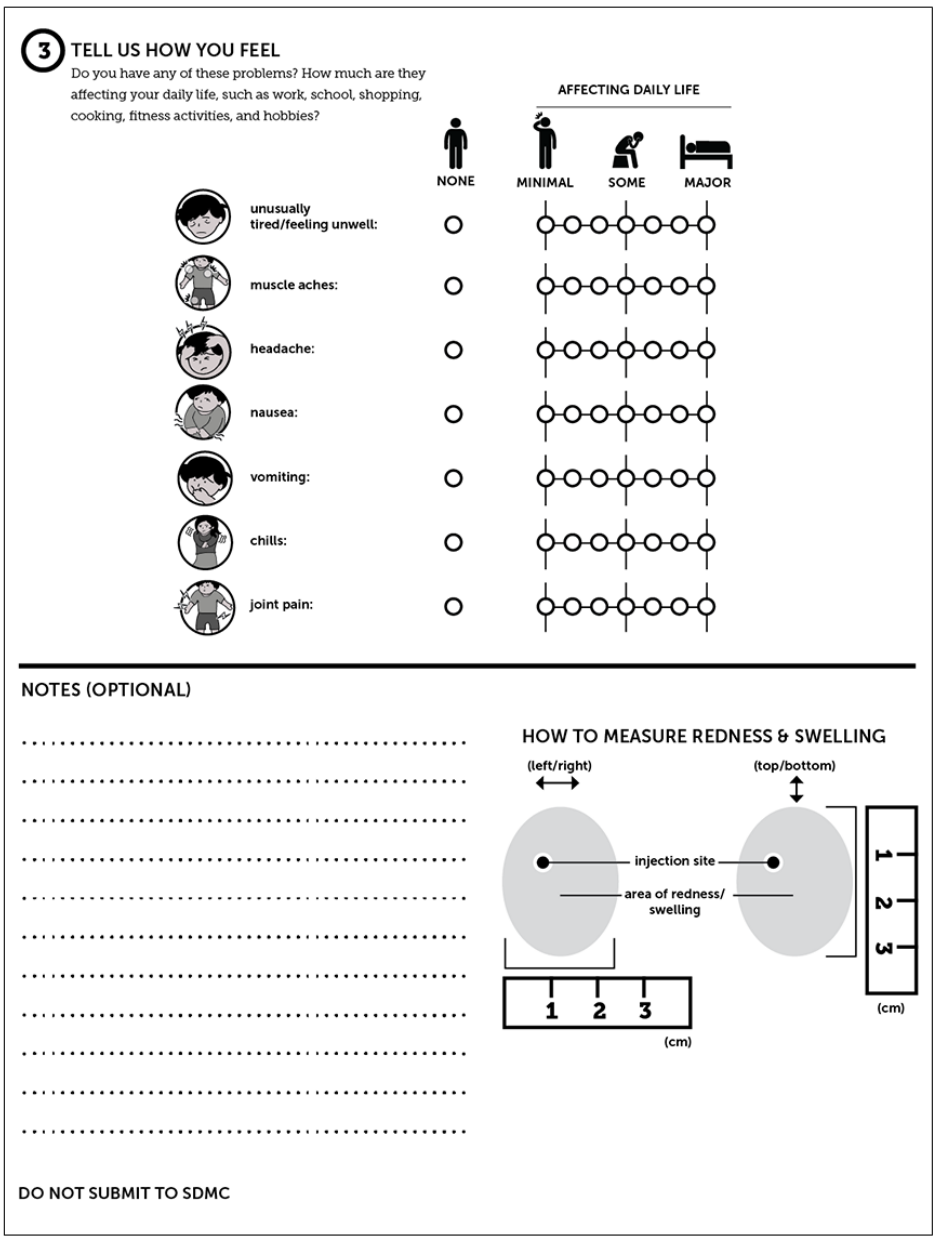
Eligibility Criteria

Participants are healthy, HIV-uninfected (seronegative) adults enrolled in the parent study, who comprehend the purpose of the study and have provided written informed consent.

The inclusion criteria are (1) HIV-uninfected male and female adults, 18 to 40 years of age, who are enrolled in the parent study at the CAPRISA ECRS; (2) participants who have confirmed full access to a compatible mobile phone and willing to receive text reminders; (3) participants who have the ability and willingness to provide informed consent; (4) participants who are English or Zulu speaking; and (5) participants who have demonstrable text message literacy.

The exclusion criteria are (1) participants who have missed vaccination visits at month 0 or 1 in the parent study; (2) participants who have had vaccination visits discontinued (temporarily or permanently); (3) participants who have mobile phones on a contractual basis, paying a monthly service and airtime fee over 24 months from purchase, as reverse billing is not compatible with this system; and (4) participants who have any significant condition or process that renders the participant incapable of participating that would interfere with or serve as a contraindication to protocol adherence, assessment of safety or reactogenicity, or a volunteer's ability to give informed consent as per the investigator's decision.

Figure 7. Sample hardcopy tool (page 3).



Blinding

Participants and site staff are unblinded as to participant intervention group assignments for the 2 arms of this study but remain blinded to the treatment assignment of the parent study. The Statistical Data Management Centre staff for the parent study are blinded to the group assignments in this nested study to maintain the integrity of the blinding for the parent study.

Follow-Up

Follow-up visits are aligned with the 2-week postvaccination safety visit of the parent study at each designated vaccination time point. At these scheduled safety visits, in addition to the parent study procedures, a computerized feasibility and acceptability survey is completed on a tablet, by both participants and research staff members. Participants have separate surveys for either the USSD tool (Multimedia Appendix 1) or hardcopy tool (Multimedia Appendix 2), while staff have one survey that compares the two (Multimedia Appendix 3).

Reactogenicity Assessments

The reactogenicity assessment period for the parent study is 7 full days following each vaccination (Tables 2 and 3). For participants assigned to the hardcopy tool arm, participants complete the tool off-site daily for 8 days (day 0 to day 7, day 0 being the night of the vaccination). Research staff contact participants daily for the first 4 days only (a phone call is made to check on the reactogenicity assessment done the day before) during the assessment period to determine whether the objective grading, as per the US National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS) adult and pediatric toxicity table [18], is confirmed. If the grading is confirmed, a repeat call the next day will be made to determine whether the symptom is resolving. If the symptom is not resolving, the participant will be brought into the clinic for a clinician assessment within 48 hours of onset of the symptom, as per the protocol. Participants document day 4 to 7 data on the tool without daily telephone review by the staff and return the tool at the 2-week postvaccination safety visit for review and reconciliation with CRFs and other site documentation. Data from the day 0 to day 3 contacts are entered directly onto the relevant CRFs during working days and into site-developed source on nonworking days. Participants are instructed to alert the site of any moderate reactogenicity symptoms on the day or any unexpected adverse events, that is, symptoms not listed in the hardcopy tool.

Table 2. Reactogenicity procedures hardcopy versus Unstructured Supplementary Service Data (USSD) tool.

Reactogenicity day	Hardcopy tool	USSD tool
Day 0	Train on use of tool, thermometer, and ruler	Train on use of tool, thermometer, and ruler; provide unique access code
Day 1	Call participant and complete source documentation for reactogenicity for day 0; enter into parent study database	Send reminder text Access database and print reactogenicity data for day 0; transcribe onto CRF[a]and enter into parent study database
Day 2	Call participant and complete source documentation for reactogenicity for day 1; enter into parent study database	Send reminder to access the USSD Access database and print reactogenicity data for day 1; transcribe onto CRF and enter into parent study database
Day 3	Call and complete source documentation for reactogenicity for day 2; enter into parent study database	Send reminder mail to access the USSD by bulk SMS[b]text messaging Access database and print reactogenicity data for day 2; transcribe onto CRF and enter into parent study database
Day 4	Call and complete source documentation for reactogenicity for day 3; enter into parent study database	Send reminder to access the USSD Access database and print reactogenicity data for day 3; transcribe onto CRF and enter into parent study database
Day 5	Call and complete source documentation for reactogenicity for day 4; enter into parent study database	Send reminder to access the USSD Access database and print reactogenicity data for day 4; transcribe onto CRF and enter into parent study database
Day 6	Call and complete source documentation for reactogenicity for day 5; enter into parent study database	Send reminder to access the USSD Access database and print reactogenicity data for day 5; transcribe onto CRF and enter into parent study database
Day 7	Call and complete source documentation for reactogenicity for day 6; enter into parent study database	Send reminder to access the USSD Access database and print reactogenicity data for day 6; transcribe onto CRF and enter into parent study database
Day 8	Call and complete source documentation for reactogenicity for day 7; enter into parent study database	Send reminder to access the USSD Access database and print reactogenicity data for day 7; transcribe onto CRF and enter into parent study database

[a]CRF: case report form.

[b]SMS: short message service.

Table 3. Schedule of reactogenicity assessments.

Day	Time	Performed by
0[a]	Baseline: before vaccination	HIV Vaccine Trials Network clinical research site staff
0	Early: 25-60 minutes after vaccination	HIV Vaccine Trials Network clinical research site staff
0	Between early assessment and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
1	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
2	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
3	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
4	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
5	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
6	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool
7[b]	Between 12:00 AM and 11:59 PM	Unstructured Supplementary Service Data or hardcopy tool

[a]Day of vaccination.

[b]New or unresolved reactogenicity symptoms present on day 3 are followed until resolution.

Participants allocated to the USSD arm are instructed to await a reminder text message daily during the 7-day reactogenicity period to access the system, enter the unique code, and complete the tool. Any symptoms reported and graded subjectively by the participant as moderate result in an immediate alert to selected research staff, via SMS text message to their mobile phones. A clinical staff member will then contact the participant by telephone to determine whether the objective grading, as per the DAIDS adult and pediatric toxicity table [18], is confirmed. If it is confirmed, the file is flagged to check the grading the next day on the database to determine whether a clinic visit is required, as per the protocol. Alerts for unexpected symptoms will also result in a site-initiated telephone contact to obtain detail, grade the symptom objectively, and facilitate reporting. Printouts from the USSD database of completed reactogenicity assessments per day will be stored in the participant binder following transcription onto a CRF and entry into the parent study database. Participants complete the USSD tool daily for 8 days on the day and at the time of the assessment; no phone calls from the site are necessary unless grade 2 or higher symptoms are reported, repeated entries are made, or the system shows that the participant has not logged in by 15:00 of the same day. If a participant misses a day, they can complete the tool retroactively for the previous day. If symptoms increase in severity after the USSD tool has been completed, it may be updated by the participant on the same day. Any dual entries on a single day prompt a call from site staff to ascertain the reason, which is documented in the site records.

Symptoms that are present at day 7 can only be detected contemporaneously and followed up in the intervention arm, allowing follow-up until resolution at a frequency determined by the investigator, for example, a call a few days later to document a resolution date. For the hardcopy tool, symptoms present at day 7 will only be known at the follow-up safety visit when the hardcopy tool is returned and reviewed or if the participant proactively alerts the site staff. If the participant does not document this in the hardcopy tool on the day that symptoms resolve, recall bias may affect the accuracy of the data when checked at the safety visit.

A backup hardcopy tool is given to all participants assigned to the USSD arm, so that in the event of technical challenges that cannot be resolved by site or provider staff, reactogenicity data are not lost to the parent study.

Termination From the Study

Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination are (1) the participant refuses further participation, (2) the participant no longer possesses a mobile phone, (3) the participant is terminated from the parent study before the vaccination series is completed, (4) the participant relocates, (5) research staff determine that the participant is lost to follow-up, (6) the investigator decides in consultation with the coinvestigator to terminate participation, for example, if a participant exhibits inappropriate behavior toward clinic staff, and (7) any condition where termination from the study is required by applicable regulations.

In the event of early participant termination from the ancillary study only, research staff would consider whether the following assessments are appropriate: a final feasibility and acceptability questionnaire with participant consent, and a reminder in the participant binder to provide a hardcopy tool at the next visit, if appropriate. Data already collected would still be used in the final analysis.

The pMOTAR may be terminated early by the determination of the parent protocol Safety Review Team, the regulatory body, the ethics committee, or the sponsor.

Social Impacts

Social impacts occur when participants experience any psychological, legal, economic, or emotional harms as a direct result of their participation in a research study; these will be reported in the parent study. The possibility of participants in this ancillary study experiencing social impacts is low to none, as data are deleted from the device automatically on submission and can only be accessed with the unique 4-digit identifying code.

Results

The USSD app has been developed and implemented. Data collection has been completed, and results will be published in a primary paper.

Discussion

Implications of the Research

If collection of reactogenicity data by the USSD tool is proven to be feasible, accessible, and superior in completeness and accuracy to the hardcopy tool, it will leverage the use of mobile phones and USSD apps for routine collection of reactogenicity data in future safety and efficacy studies of vaccine candidates, and in eventual programmatic rollout. Our experience in development and implementation of the USSD app will allow for adjustments to any future development and implementation in order to reduce challenges and facilitate seamless collection of data across all sites and studies, with appropriate training. If successful, it will facilitate contemporaneous reactogenicity data capture, while improving efficiency and accuracy. Accurate safety data collection may allay participant and public fears of side effects, leading to increased uptake of HIV vaccines in research studies, and eventually in programmatic rollout. Improved uptake will contribute to producing the herd immunity required to ensure a halt to transmission in endemic areas.

Strengths and Limitations

Using a randomized controlled clinical trial to assess feasibility, accessibility, completeness, and accuracy of the USSD is a key strength of this study. Ensuring that the USSD and hardcopy tools collect exactly the same safety data means that the safety end points and potential impact on the objectives and analysis of the parent study are not compromised. Unlike the hardcopy tool, the USSD tool cannot be lost, even if the mobile phone is lost, because the data having been uploaded to the database will still be available for entry onto CRFs. From a technology innovation perspective, the selection of USSD as the delivery mechanism for the intervention is an added strength, based on accessibility on any basic mobile phone. Contemporaneous alerts to research staff of moderate symptoms allows for real-time follow-up to ensure symptoms are resolving and to assess whether a clinic assessment is required or a parent study pause rule has been met. Erroneous temperature data can also be immediately identified, and the participant can be contacted in a timely manner to repeat the measurement. The USSD unique code increases the likelihood that the participant is completing the data; the prepopulation of the user, dates, and times recorded by the system on log-in removes duplication of data fields for possible error, thus improving the overall quality of the data. Data can be accessed in real time by staff and transcribed onto CRFs, facilitating earlier entry into the parent study database. Confidentiality is assured by autodeletion of any data entries after completion of a USSD string and submission to the tool database, averting the possibility of social harm. Preservation of the last active screen builds in efficiency, so that a participant does not double enter data for the same data field erroneously.

Limitations include that the study is not blinded, in terms of allocation of intervention; however, data analysis staff at the Statistical Data Management Centre will be blinded to the allocation at the time of analysis of the parent study safety data, thus maintaining the integrity of the parent study blinding. Errors in USSD entry cannot be corrected in real time without a duplicate entry on the same or next day. The USSD tool is limited to text only, and the lack of graphical representations, including the use of bold typeface and color, reduces the attractiveness of the user interface, as well as the appeal to participants who respond to graphics more easily than text. Technological challenges when the network signal is poor or handsets are not fully charged are also potential limitations, as is the recruitment from only 1 site and the small sample size, which reduces the generalizability of this study and the reliability of the answer. It is possible that countries with lower mobile phone coverage and access may have reduced text literacy, which would affect the utility of the tool across regions.

Conclusion

This is, to our knowledge, the first South African randomized clinical trial to test the feasibility and accessibility of the USSD tool for collection of reactogenicity data in an HIV vaccine trial, and to attempt to prove superior accuracy and completion to the hardcopy tool. This would, we hope, improve the reliability of safety data and possibly increase uptake of vaccines through accurate reporting of safety data.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey for participants on acceptability of the pilot study of Mobile Technology to Assess Reactogenicity (pMOTAR) app.

[PNG File, 202KB - resprot_v7i10e175_app1.png]

Multimedia Appendix 2

Survey for participants on acceptability of the hardcopy tool.

[PNG File, 188KB - resprot_v7i10e175_app2.png]

Multimedia Appendix 3

Survey for staff members on acceptability of the pilot study of Mobile Technology to Assess Reactogenicity (pMOTAR) app.

[PNG File, 264KB - resprot_v7i10e175_app3.png]

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Abbreviations

CAPRISA: Centre for the AIDS Programme of Research in South Africa

CRF: case report form
DAIDS: Division of AIDS
ECRS: eThekwini Clinical Research Site
HVTN: HIV Vaccine Trials Network
mHealth: mobile health
SMS: short message service
USSD: Unstructured Supplementary Service Data

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Protocol

Varenicline and Bupropion for Long-Term Smoking Cessation (the MATCH Study): Protocol for a Real-World, Pragmatic, Randomized Controlled Trial

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Abstract

Background: Varenicline and bupropion are efficacious, prescription-only pharmacotherapies for smoking cessation; however, their real-world impact is limited by prescriber knowledge, affordability, and accessibility.

Objective: The primary objective of the MATCH (Medication Aids for Tobacco Cessation Health) study was to evaluate the real-world, long-term effectiveness of mailed bupropion and varenicline in a sample of interested smokers with the utilization of Web-based recruitment and follow-up. In addition, the study aims to investigate the genotypic and phenotypic predictors of cessation.

Methods: This is a two-group, parallel block, randomized (1:1) open-label clinical trial. This study will be conducted online with the baseline enrollment through the study's website and follow-up by emails. In addition, medication prescriptions will be filled by the study contract pharmacy and couriered to participants. Individuals who smoke ≥10 cigarettes per day and intend to quit within the next 30 days will be recruited through Public Health Units and Tobacco Control Area Networks throughout Ontario by word-of-mouth and the internet. Eligible participants will receive an email with a prescription for 12-week assigned medication and a letter to take to their physician. The recruitment and randomization will continue until 500 participants per arm have received medication. All participants will receive weekly motivational emails during the treatment phase. The primary outcome measure is the smoking status after 6 months, biochemically confirmed by mailed-in salivary cotinine. Follow-ups will be conducted through emails after 4, 8, 12, 26, and 52 weeks of starting the treatment to assess the smoking prevalence and continuous smoking abstinence. In addition, mailed-in saliva samples will be used for genetic and nicotine metabolism analyses. Furthermore, personality characteristics will be assessed using the Big Five Aspect Scales.

Results: The project was funded in 2014 and enrollment was completed in January 2017. Data analysis is currently underway.

Conclusions: To the best of our knowledge, this is the first randomized controlled trial to mass distribute prescription medications for smoking cessation. We expect this method to be logistically feasible and cost effective with quit outcomes that are comparable to published clinical trials.

Trial Registration: ClinicalTrials.gov NCT02146911; https://clinicaltrials.gov/ct2/show/NCT02146911 (Archived by WebCite at http://www.webcitation.org/72CZ6AvXZ)

Registered Report Identifier: RR1-10.2196/10826

(JMIR Res Protoc 2018;7(10):e10826) doi:10.2196/10826

KEYWORDS

bupropion; genetics; internet; personality traits; smoking cessation; tobacco; varenicline

Introduction

Background

The prevalence of tobacco smoking in developed countries has steadily declined over the past three decades. However, with 16% of the general Canadian population aged ≥15 years [1], the prevalence of smoking remains a formidable cause of mortality and morbidity in Canada. The burden of tobacco use is high, resulting in Can $17 billion in direct and indirect costs to the Canadian economy [2]. Clinical interventions are an important component of comprehensive tobacco control strategies [3]. Nicotine replacement therapy, bupropion, and varenicline are proven to be efficacious pharmacological aids, doubling the chances of success in quitting smoking [4-6].

To date, 3 randomized controlled trials (RCTs) have compared varenicline, bupropion, and placebo [6-8]. The primary outcome measure was continuous abstinence rates (CARs) at various time points as follows: weeks 9-12 (end of treatment), weeks 9-24 (6-month time point), and weeks 9-52 (1-year time point). Only one trial reported a significant difference in CARs after 52 weeks [7] with varenicline having significantly higher long-term abstinence rates than bupropion (23% vs 14.6%, respectively; odds ratio [OR] 1.77, 95% CI 1.19-2.63, *P*=.004). However, an identical clinical trial conducted in parallel with the same sample size [6] did not show a significant difference in CARs between varenicline (21.9%) and bupropion (16.1%; OR 1.46, 95% CI 0.99-2.17, *P*=.06) after 52 weeks.

Therefore, although there is limited evidence for the superior long-term efficacy of varenicline, no study has assessed the real-world effectiveness of these medications for long-term abstinence. This is important because of some significant differences between clinical trials and real-world settings, which could influence cessation treatment outcomes; for example, clinical trials have strict eligibility criteria, excluding participants with certain comorbidities. Therefore, participants in these studies are in better health compared with the general population. In addition, treatment with medications in clinical trials is accompanied by one-on-one smoking cessation behavioral counseling often on a weekly basis, which is largely unavailable in real-world settings [7]. These factors together have the potential to restrict the external validity of clinical trial findings. As such, there is a need to assess the real-world effectiveness of these prescription medications at a population level to further strengthen the evidence base for the effective treatment of tobacco dependence.

Even though proven efficacious in clinical trials, according to the Canadian Tobacco Use Monitoring Survey in 2007, less than half of smokers who have ever attempted to quit have used a smoking cessation aid [9]. Most of these smokers identify the lack of access to adequate and evidence-based information, in addition to the cost, as reasons for not using these smoking cessation pharmacotherapies [9]. Furthermore, bupropion and varenicline are only available by a prescription from a licensed practitioner. Therefore, in addition to knowledge and affordability, their population-level impact is limited by accessibility. Furthermore, smoking cessation clinics are limited in number, and a survey conducted in Canada demonstrated that the occurrence of smoking cessation discussion between physicians and patients is not common. In fact, of 88% of smokers who visited a primary care physician in the year prior, only half received any advice on quitting or reducing smoking [10]. Efforts to address these barriers could greatly improve the use and effectiveness of these smoking cessation medications in real-world settings [11]. Furthermore, mass distribution approaches, bypassing clinics and physicians, have been successful for nicotine replacement therapy [12,13]. However, bupropion and varenicline have the potential to make a greater impact, given their superior results from clinical trials.

Study Aims

The primary aim of this large RCT is to assess the long-term cessation rates associated with bupropion and varenicline treatment using the internet as a novel approach. Secondary aims include investigating the pharmacogenetic factors and phenotypic characteristics affecting nicotine dependence and smoking cessation outcomes.

Hypotheses

The hyphotheses of the study are as follows: the long-term abstinence rates (at 6-month follow-up) will be significantly higher in the varenicline group than in the bupropion group; the overall quit rates will be similar to those reported from traditional RCTs; and specific genotypes and phenotypes of individuals will influence smoking treatment outcomes.

Methods

Study Design

The Medication Aids for Tobacco Cessation Health (MATCH) study is an internet-based pragmatic randomized clinical trial. This study is open-label, wherein eligible participants are randomly assigned to study medication, bupropion (Zyban) or

varenicline (Champix), for 12 weeks in conjunction with weekly motivational emails. All participants will receive medication plus an identical email-based behavioral intervention. The research methods and protocol for this study have been approved by the standing Research Ethics Board (REB) at the Centre for Addiction and Mental Health (CAMH) with the reference number 200/2012. This study is registered at ClinicalTrials.gov (NCT02146911). Figure 1 shows a CONSORT (Consolidated Standards of Reporting Trials) diagram for the study outlining estimates for the recruitment and dropout. The figure illustrates the estimated participant flow of the proposed intervention trial. It demonstrates the expected participant numbers in the enrollment and study completion processes. The estimated number of participants active at each stage of the study are estimated based on the pilot study conducted previously [14].

Setting

Web-Based Consent, Self-Assessment, and Automated Eligibility Determination

Figure 2 shows the flowchart of participants through different components of the study. It includes the enrollment process, followed by randomization, mailing of the medication, and follow-up surveys completed at various time points.

Interested individuals will visit the study website and read a brief description of the study purpose, its procedures, and treatments provided. Those interested in participating will read the study information and consent form and provide their consent by clicking "yes" on the study website; they may also indicate whether they would like to be contacted for future studies. Individuals are permitted to participate in the study even if they do not give consent to be contacted for future studies. After completing the consent form, participants will complete the baseline survey, which will take approximately 20 minutes. The baseline questionnaire collects information on demographics, socioeconomic factors, education, ethnicity, smoking habits (cigarettes smoked per day, duration of daily smoking, and when participants first began smoking), importance and confidence to quit, substance and alcohol usage, concurrent usage of other medication(s), and any psychiatric comorbidities (ie, depression, anxiety, and schizophrenia).

In addition, if eligible, participants will be asked if they consent to provide a saliva sample for the genetic testing component of the study. If they agree to enroll in this substudy, they will complete the Big Five Aspect Scale personality test online through the study website, which will take approximately 10-15 minutes. Big Five Aspect Scale is a self-reported public domain test, which assesses the big 5 personality traits by asking 100 questions answered on a 5-point scale ranging from "strongly disagree" to "strongly agree" [14]. Individuals will be permitted to take part in the efficacy study even if they do not consent to participation in the genetics substudy. The questionnaires used have been published previously and include the Fagerstrom test for nicotine dependence [15], the BFAs for accessing the big 5 personality traits—extraversion, neuroticism, conscientiousness, agreeableness, and openness to experience [14]—and Patient Health Questionnaire for the evaluation of depression [16]. These questionnaires have been widely used in clinical studies, involving smoking, and extensively validated [14-16].

Figure 1. An overview of the proposed intervention trial (CONSORT [Consolidated Standards of Reporting Trials] diagram).

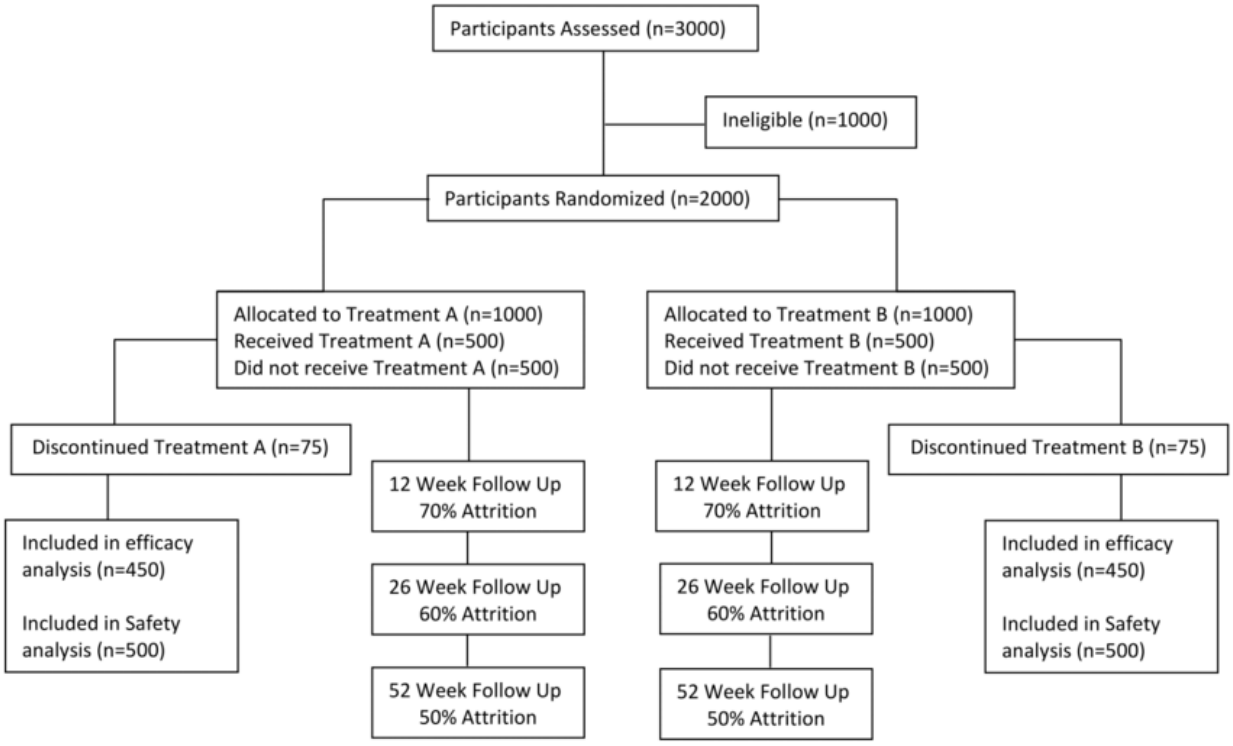
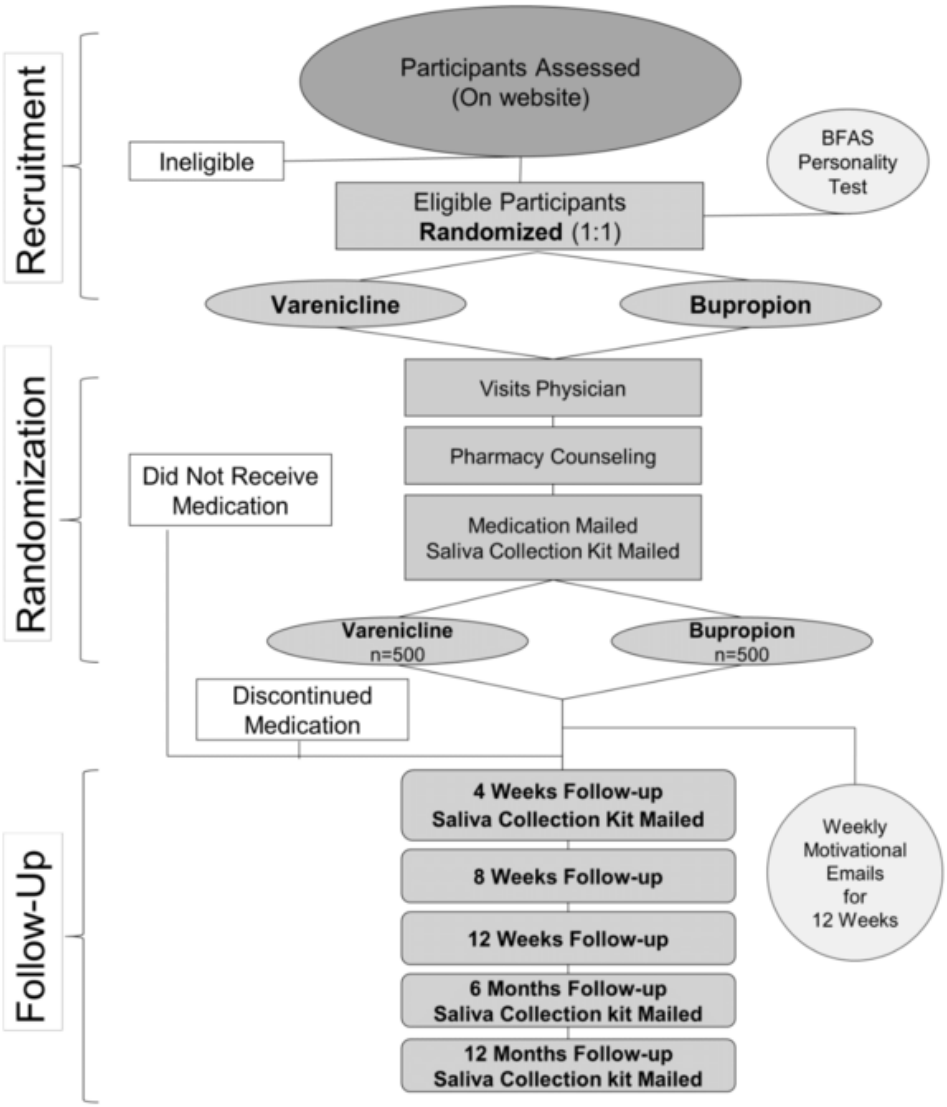


Figure 2. Participants' flowchart. BFAS: Big Five Aspect Scale.



After submitting the completed questionnaires, individuals will be notified, through an on-screen message, whether they are eligible for the study. Those who are eligible will receive an email, including their medication assignment, the study information and consent form, a standardized letter to the doctor to convey information about the study, and a standard script for the study medication they have been assigned to for their physician (or other licensed prescriber) to sign. Because there are no in-person study visits, Salivette kits will be mailed out at the time of study enrollment to verify the participants' smoking status.

In addition, baseline saliva sample will be used to measure the nicotine metabolite ratio, which is the ratio of 3'-hydroxycotinine and cotinine (COT) concentration; this is a validated phenotypic biomarker of the CYP2A6 enzyme activity [17]. Furthermore, Salivette kits will be sent at weeks 4, 26, and 52 to measure the salivary COT level for the biochemical verification of abstinence. Those who consent to the genetics substudy will receive a second email with the genetics study information and consent form and the Oragene saliva DNA kits by mail to collect a DNA sample for the pharmacogenetics component of the study. Participants will be compensated for each DNA (if applicable) and subsequent saliva samples received.

Patient Visit to a Licensed Practitioner

All eligible participants will be required to visit their physician or another licensed prescriber within 5 weeks from the enrollment date to sign the prescription for their assigned medication. Reminder emails will be sent after 2 weeks of the enrollment date to make sure that the participants have booked an appointment to visit their practitioner. At the visit, participants will discuss their medical history, the medications they are on, and any other concerns they have regarding the treatment. At his or her discretion, a licensed practitioner may either sign the prescription for study medication or choose not to prescribe the assigned medication to their patient. The practitioner's office will then fax the signed prescription to a mail-order pharmacy contracted to do the study that will then fill the prescription.

Mail-Out Pharmacy

Prescriptions signed by a licensed practitioner and verified to be authentic will be filled and mailed to the participants'

addresses by the contract mail-order pharmacy. In accordance with the Ontario College of Pharmacists' standard of practice, pharmacists will call each study participant at the time of dispensing (ie, mailing) the medication to inform participants about directions to use the medication, discuss possible allergies, concomitant medications, and offer counseling.

Participants

Inclusion and Exclusion Criteria

The following inclusion criteria will need to be met before any individual is randomly assigned to one of the 2 treatment arms: Ontario resident; having a valid email address; aged at least 19 years; current daily smoker; smoking at least 10 cigarettes per day; smoked daily for at least the past year; and have an intention to quit smoking within 30 days of receiving the medication. The following are criteria that will exclude an individual from being randomly assigned to one of the 2 treatment arms: a history of psychotic disorder (schizophrenia or bipolar disorder) or eating disorder; brain injury; seizure disorder; pregnancy, lactation, or at risk of becoming pregnant; allergy or sensitivity to bupropion or varenicline; or currently taking varenicline or Champix, bupropion or Zyban or Wellbutrin, monoamine oxidase inhibitors, thioridazine, antidepressants, or other medications containing bupropion hydrochloride.

Recruitment and Randomization

The primary method of recruitment for this study will be by word-of-mouth through family, friends, or health care providers. The Smoking Treatment for Ontario Patients Study [12,13], also conducted by the investigators of this trial, has successfully built a collaborative network of providers from public health units, community health centers, family health teams, and community pharmacies across Ontario. This network of providers has proven to be effective in disseminating new treatment opportunities to smokers in their area. Interested individuals will self-identify and will be directed to enroll through the study website. Moreover, as part of the consenting procedure for those who participated in the Smoking Treatment for Ontario Patients Program, individuals will be asked whether they would like to be contacted about new research opportunities by CAMH. Those who choose "yes" will then be included in a database forming a smokers' registry that can be contacted in case new research opportunities come up. This smokers' registry will be another method of recruitment used for this study. Furthermore, the public will be informed about the study through CAMH social media accounts, Smokers' Helpline, and Facebook advertisements.

Randomization

Eligible participants will be randomly assigned to one of the 2 study arms (varenicline or bupropion). Permuted block randomization in a 1:1 ratio in blocks of 100 will be employed. The randomization process will be computerized. Owing to the large proposed sample size in this study, there will be no stratification or minimization.

Current Recruitment Status

Study recruitment is no longer active; however, there are still few 1-year follow-ups that are yet to be completed by participants.

Retention Strategies

Weekly motivational emails and payment for mailed-in saliva samples at the 4-week time point will be used to encourage treatment fidelity and maintain engagement in the study.

Sample Size

In the 2 head-to-head RCTs of varenicline versus bupropion [6,7], participants were randomized 1:1:1 to varenicline, bupropion, or placebo arms with 341-345 participants in each group. In the trial conducted by Gonzales et al [6], the 9- to 52-week CARs were 21.9% in the varenicline group versus 16.1% in the bupropion group (OR 1.49, 95% CI 0.99-2.17, *P*=.057). In the trial conducted by Jorenby et al [7], the 9- to 52-week CARs were 23% in the varenicline group compared with 14.6% in the bupropion group (OR 1.77, 95% CI 1.19-2.63; *P*=.004). Because this is an effectiveness trial, we anticipate lower quit rates overall. Indeed, in our previous feasibility study [18], 7-day point prevalence abstinence (PPA) rates after 6 months (intention-to-treat analysis) were 18.9% in those who received varenicline and 17.4% in those who received bupropion.

To be sufficiently powered to detect a significant difference in the 26-week CARs, we plan to randomize 500 subjects to each medication arm. We predict that the real-world abstinence rates will be slightly lower than those observed in clinical trials and may be similar to what we found in our nonrandomized study that this protocol is based on [19]. Therefore, we assumed that the 26-week CAR in the varenicline-treated group would be 20% compared with 15% in the bupropion-treated group. At 500 subjects per group, we will have 80% power to detect a significant difference between groups at a .05 level of significance.

Blinding

This is an open-label, clinical trial; therefore, the procedures will not be blinded because participants will need to visit their physician to approve their randomized medication. Pharmacists, primary care providers and research personnel will know which medication participants have been assigned to.

Medication

Compliance with the prescribed regimen will be measured by participants' self-report follow-up assessments at weeks 4, 8, and 12. In addition, saliva sample kits will be mailed out to participants at week 4 for the biochemical analysis of drug levels to confirm medication compliance. Participants will be compensated for each sample received.

Behavioral Support

All eligible participants will receive 12 weekly motivational emails for the duration of treatment. The emails include tips on several things, other than the medications, which participants can do to help them quit smoking. The contents of the emails vary from week to week (Multimedia Appendix 1).

Participant Follow-Up by Email

Participants will be contacted by email at weeks 4, 8, 12, 26, and 52 to complete follow-up surveys. The follow-up surveys will collect data on changes to the participants' smoking pattern and medication use and any possible adverse reactions experienced. During each follow-up survey, participants will be asked whether they have experienced any adverse events. If the participants at any point are experiencing intolerable adverse events, they can contact the study personnel to withdraw from the study. They will be compensated for all the saliva and genetic samples that they had submitted prior to being withdrawn. There will be no modifications to interventions even if adverse side effects are reported. Instead, participants will either be discontinuing their treatment or will be advised to speak with their physician regarding the intervention. If participants withdraw from the study, they will still be asked to complete follow-up surveys.

Cost-Effectiveness

To make an impact on the prevalence of smoking in the overall population, it is necessary for an intervention to reach a high number of people. Efficacious pharmacotherapies are available for smoking cessation but their reach is typically limited. To the best of our knowledge, this is the first study to attempt the mass distribution of prescription medications for smoking cessation using a randomized study design. The method proposed has been previously demonstrated by the investigators of this study to be logistically feasible and effective in terms of cessation rates [18] and has provided crucial evidence for an approach that has the potential to make a significant impact on cessation rates at a population level by demonstrating a way to take full advantage of the available smoking cessation aids.

All recruitment, consenting, and data collection are Web-based. The mail-order pharmacy is less expensive than dispensing through a research pharmacy, and we do not need to pay physicians to recruit their patients into studies because subjects self-identify first and then go to their physician (in Canada, all physician visits are paid for by our universal health care system). As such, this large randomized trial can be extremely cost effective with an estimated cost of under Can $150,000. We aim to provide medication to 1000 participants; therefore, the cost per enrollment is estimated to be Can $133.33. The 52-week CAR in the varenicline-treated group is assumed to be 18% compared with 12.5% in the bupropion group. Therefore, the cost per quit is estimated to be about Can $873.36 plus Can $33.70 for a visit to the prescriber if the government's universal health plan is billed; this is much lower compared with the economic burden of continued smoking. A report published in 2015 estimated the annual health care cost in Canada to be Can $3071 per smoker [20].

Primary Outcome

The primary outcome measures will be related to the effectiveness of treatment. The primary outcome will biochemically confirm 30-day continuous abstinence by mailed-in salivary COT 26 weeks after the start of treatment. Secondary outcome variables will be self-reported 30-day continuous abstinence at the end of the treatment (weeks 9-12) and at weeks 26 and 52; this is defined as not having smoked, even a puff, in the past 30 days and lack of relapse during this period. Other outcome variables include self-reported 7-day PPA measured at weeks 4, 8, 12, 26, and 52. The 7-day PPA is defined as not having smoked, even a puff, over the last 7 days.

Exploratory Measures and Potential Covariates

The tertiary outcome measures will be related to variations in genetic polymorphisms, metabolic factors, and personality traits observed in each treatment group. A 3-way analysis looking at the interaction between genetic polymorphism and treatment outcome, personality traits and treatment outcome, and genetic polymorphism and personality traits will be conducted; this part of the study should be considered exploratory. We have no specific hypotheses currently.

Data Access

Datasets will only be available to CAMH research personnel only or those involved in the study. The funder does not have access to the trial dataset. Currently, there is no ability for the study data to be openly accessed by other researchers because of the restrictions placed by our REB.

Data Analysis

Analysis of study results will be conducted using the intention-to-treat analysis, wherein all participants who are randomized to a treatment arm and receive their assigned medication are included in the final analysis whether they complete the study or respond to follow-up surveys at study end points. This method will be used to avoid any bias that can potentially arise because of crossover and dropouts, affecting the initial random assignment to treatment groups. Participants who are lost to follow-up or do not provide a saliva sample for the COT confirmation of abstinence will be considered as smokers according to recommendations by the Society for Research on Nicotine and Tobacco's subcommittee on Biochemical Verification (2002) [21].

The baseline characteristics will be analyzed and compared between intervention groups using the Student's *t* test for continuous variables and cross-tabs chi-square analysis for all categorical variables. Any characteristics that differ significantly across our 2 study groups will be included as covariates in all subsequent analyses. The effect of intervention over time will be evaluated using the longitudinal logistic regression analysis with abstinence as the dependent variable and treatment condition along with other baseline characteristics as independent predictors. We will construct a longitudinal generalized estimating equations (GEE) model for each binary outcome. GEE is a suitable analysis method because it accommodates for the statistical dependence among repeated observations within subjects. Because our primary outcome is abstinence from smoking (Yes or No) at each follow-up time point, GEE is appropriate because it allows for the estimation of population-averaged effects while accounting for the dependencies among the repeated measures. The data analysis for this study will be overseen by the principal investigator in consultation with the Biostatistical Consulting Service at CAMH.

Results

The project was funded in 2014 and enrollment was completed in January 2017. Data analysis is currently underway and the first results are expected to be submitted for publication in October 2018.

Discussion

The proposed trial on providing free medication mailed to smokers is expected to be cost effective and will be useful for policy makers to consider as part of a comprehensive tobacco control strategy. This can help reduce the prevalence of smoking and its related costs to our health care system and the overall economy. With the knowledge gained, the method can be modified according to the peculiarities of other health care jurisdictions to impact the smoking prevalence in those areas as well.

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Authors' Contributions

LZ, BLF, and PS conceived and designed the study and obtained the funding. LZ and TM-G completed all initial study design material. TM-G and HZ were major contributors in writing the manuscript. BLF and PS were contributors in editing the manuscript.

Conflicts of Interest

Over the last 5 years, PS has received grants from Pfizer Inc, Shoppers Drug Mart, Bhasin Consulting Fund Inc, and Patient-Centered Outcomes Research Institute. BLF receives support from Pfizer Global Research Awards in Nicotine Dependence Award Program.

Multimedia Appendix 1

Example emails of MATCH weekly motivational messages.

[PDF File (Adobe PDF File), 270KB - resprot_v7i10e10826_app1.pdf]

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Abbreviations

CAMH: Centre for Addiction and Mental Health
CAR: continuous abstinence rate
CONSORT: Consolidated Standards of Reporting Trials
COT: cotinine
GEE: generalized estimating equation
MATCH: Medication Aids for Tobacco Cessation Health
OR: odds ratio
PPA: point prevalence abstinence
RCT: randomized controlled trial
REB: Research Ethics Board

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Protocol

Effects of Transcranial Direct Current Stimulation on Knee Osteoarthritis Pain in Elderly Subjects With Defective Endogenous Pain-Inhibitory Systems: Protocol for a Randomized Controlled Trial

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Abstract

Background: Knee osteoarthritis (OA) has been the main cause behind chronic pain and disabilities in the elderly population. The traditional treatment for knee OA pain currently concerns a number of combinations of pharmacological and nonpharmacological therapies. However, such combinations have displayed little effects on a significant group of subjects. In addition to this, pharmacological treatments often cause adverse effects, which limits their use on this population. Previous studies showed that chronic knee OA pain may be associated with maladaptive compensatory plasticity in pain-related neural central circuits indexed by a defective descending pain-inhibitory system. Transcranial direct current stimulation (tDCS) can revert some of these maladaptive changes, thus decreasing chronic pain sensation. Numerous studies have demonstrated that the use of anodal tDCS stimulation over the primary motor cortex (M1) has positive effects on chronic neuropathic pain. Yet, data on OA pain in elderly patients, including its effects on the endogenous pain-inhibitory system, remain limited.

Objective: The objective of this study is to evaluate the efficacy of tDCS in reducing pain intensity caused by knee OA in elderly subjects with defective endogenous pain-inhibitory systems.

Methods: We designed a randomized, sham-controlled, single-center, double-blinded clinical trial. Patients with knee OA who have maintained a chronic pain level during the previous 6 months and report a pain score of 4 or more on a 0-10 numeric rating scale (NRS) for pain in that period will undergo a conditioned pain modulation (CPM) task. Participants who present a reduced CPM response, defined as a decrease in NRS during the CPM task of less than 10%, and meet all of the inclusion criteria will be randomly assigned to receive 15 sessions of 2 mA active or sham tDCS for 20 minutes. A sample size of 94 subjects was calculated. The Brief Pain Inventory pain items will be used to assess pain intensity as our primary outcome. Secondary outcomes will include pain impact on functioning, mobility performance, quality of life, CPM, pressure pain threshold, touch-test sensory evaluation,

and safety. Follow-up visits will be performed 2, 4, and 8 weeks following intervention. The data will be analyzed using the principle of intention-to-treat.

Results: This study was approved by the institutional review board with the protocol number 1685/2016. The enrollment started in April 2018; at the time of publication of this protocol, 25 subjects have been enrolled. We estimate we will complete the enrollment process within 2 years.

Conclusions: This clinical trial will provide relevant data to evaluate if anodal tDCS stimulation over M1 can decrease chronic knee OA pain in elderly subjects with defective CPM. In addition, this trial will advance the investigation of the role of central sensitization in knee OA and evaluate how tDCS stimulation may affect it.

Trial Registration: ClinicalTrials.gov NCT03117231; https://clinicaltrials.gov/ct2/show/NCT03117231 (Archived by WebCite at http://webcitation.org/73WM1LCdJ)

International Registered Report Identifier (IRRID): RR1-10.2196/11660

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KEYWORDS

transcranial direct current stimulation; elderly; chronic pain; knee osteoarthritis; conditioned pain modulation

Introduction

Osteoarthritis (OA) is the most common cause of pain and disabilities in elderly populations, and the knee is the most commonly affected joint [1,2]. OA is a disease characterized by cell stress and extracellular matrix degradation that stimulates maladaptive repair responses as proinflammatory pathways of innate immunity [3]. It has been determined that 33.6% of individuals older than 65 years suffer from OA, and 10% of individuals aged 60 years and older have symptomatic knee OA [4]. Subjects with chronic knee OA pain may experience depressive symptoms, sleep disorders, functional dependency, and a decrease in life quality, and this can have a subsequent impact on public health system costs [5]. OA knee pain is traditionally managed with a combination of pharmacological and nonpharmacological therapies including weight loss, physical therapy, several exercise modalities, anti-inflammatory drugs, topical agents, and opioids analgesics [6]. Although these treatments can decrease the pain intensity, they can also lead to substantial adverse effects (eg, dizziness, dry mouth, constipation, and nausea), and the treatment benefits may decrease over time (eg, opioid tolerance development) [7-9]. Previous studies suggested that peripheral and central sensitization are two of the underlying mechanisms in OA pain that can lead to lower pain thresholds, hyperalgesia, and spatial summation in asymptomatic areas [10,11].

Peripheral sensitization is caused by changes in the physiology of peripheral nociceptors due to localized inflammation. At the central level, there is an imbalance in endogenous pain modulation, characterized by a greater facilitation of pain and a reduced capacity to inhibit pain [12]. In addition, the aging process is associated with a dysregulation in the central modulation of pain, potentially placing elderly patients at a greater risk of chronic pain [13,14]. Conditioned pain modulation (CPM) is one of the most studied dynamic quantitative sensory tests; CPM is related to the reduction of pain produced by a test stimulus in response to a second noxious conditioning stimulus on a remote body side [15-17]. Previous studies showed that the pain reduction during CPM testing in healthy adults is approximately 23%, while in the healthy elderly population the reduction is approximately 17% [18,19]. A recent study indicated that elderly individuals with chronic pain due to severe osteoarthritis may have a significant dysfunction in the descending control of nociceptive processing, as the pain reduction during a CPM task is less than 10% [20].

In support of the above mentioned central sensitization mechanism, the rationale for treatment should also aim to modulate central nervous system plasticity [21,22]. Although drugs can change brain plasticity, their effects are more diffuse, which limits results. Moreover, as pharmacological treatments to chronic pain often lead to intolerable side effects in elderly patients, there is an increasing interest in nonpharmacological intervention options [23-25]. Transcranial direct current stimulation (tDCS) is a powerful noninvasive technique to modulate cortical excitability using a weak direct current applied through the scalp in a painless way; its prolonged and continuous application can induce neuroplasticity [26,27]. These changes depend on the polarity of the montage, with anodal stimulation enhancing excitability and cathodal stimulation decreasing excitability [28]. tDCS has shown positive effects on chronic pain in some diseases, which indicates that it may revert maladaptive plasticity associated with chronic pain sensation [29,30]. For pain, the most effective cortical target is the primary motor cortex (M1), a gateway to deep pain-related networks such as thalamic nuclei [31,32]. Previous brain imaging studies showed a positive cortical and subcortical neurophysiologic response to tDCS with anode over M1 and cathode over contralateral supraorbital region [33,34]. A recent trial showed that tDCS over the motor cortex might increase CPM response [35]. Another recent pilot trial evaluated the effect of tDCS on clinical pain severity for older adults with knee OA; it did not display consistent results in all pain assessments, yet their preliminary results showed promising clinical efficacy [36].

The aim of this trial is to assess the effects of tDCS on the intensity of pain in elderly patients suffering with OA knee chronic pain. We chose to test these effects in aged people with defective endogenous inhibitory pain systems, as the previous data showed increased therapeutic response in this population [37,38]. As secondary outcomes, we will evaluate the safety of tDCS and the changes in quality of life, pain impact on

functioning, CPM, pressure pain threshold, touch-test sensory evaluation, and mobility performance.

Methods

Study Design

We will conduct a single-center, double-blinded, randomized, and controlled parallel clinical trial. The study was approved by the Ethics Committee of São Paulo Hospital (HSP) with the protocol number 1685/2016 and has been registered with ClinicalTrials.gov (NCT03117231). The trial will be performed at the Federal University of São Paulo, Brazil, and will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) [39]. Participants will agree to the participation by signing the informed consent. They will be allowed to leave the study at any time without negative repercussions.

Participants

Individuals aged 60 years and older, which is the definition for the elderly in Brazil [40], with an established diagnosis of unilateral or bilateral knee OA as established by the American College of Rheumatology criteria of 1986, using history, physical examination, and radiographic findings according to the Kellgren-Lawrence radiographic grading, will be recruited [41]. Patients will be recruited from HSP and from all the outpatient clinics belonging to the Federal University of São Paulo. Eligible subjects will have had pain in the knee for a minimum of 6 months, with an average pain score of 4 or more on a 0-10 numeric rating scale (NRS) for pain over that period and during the week prior to the first stimulation session. Following this, the subjects will be required to report a reduction on NRS during the CPM task of less than 10% compared to the pain score before the test.

Exclusion criteria include patients who have any severe acute or chronic uncompensated disease (such as uncontrolled hypertension, diabetes, cardiac issues, heart failure, or chronic obstructive pulmonary disease), history of epilepsy or syncope, contraindications to transcranial brain stimulation (ie, implanted brain medical devices or implanted brain metallic devices), established cognitive impairment, history of fractures in the lower limbs and/or spine in the last 6 months, traumatic brain injury with residual neurological deficits, alcohol abuse within the last 6 months as self-reported, use of carbamazepine within the last 6 months as self-reported, or severe depression (with a score of more than 30 on the Beck Depression Inventory). The principal investigator will obtain informed consent prior to enrolling participants in the study. We expect in this elderly population to have a female-to-male ratio of about 70%:30%.

In order to avoid drop outs, the principal investigator will follow up with all participants by phone during the entire study to remind them of the schedule. Participants and treating physicians will be told that changes in treatment during the study are strongly discouraged and must be reported. In addition, no treatment crossover will be permitted.

Randomization and Blinding

We will use a computer-generated list to randomize subjects to one of the two treatment arms: active transcranial direct current stimulation (tDCS-a) or sham transcranial direct current stimulation (tDCS-s). The participants will be randomized with a ratio of 1:1 to either group using randomized block sizes (4 and 6) and stratified by severity of pain (less than 7 and 7 or more). The randomization will be concealed in consecutively numbered, sealed opaque envelopes and will be performed by an investigator not involved in the assessments or the recruitment. The participants and investigators who will perform the evaluation will be completely blinded until completion of the study and data processing.

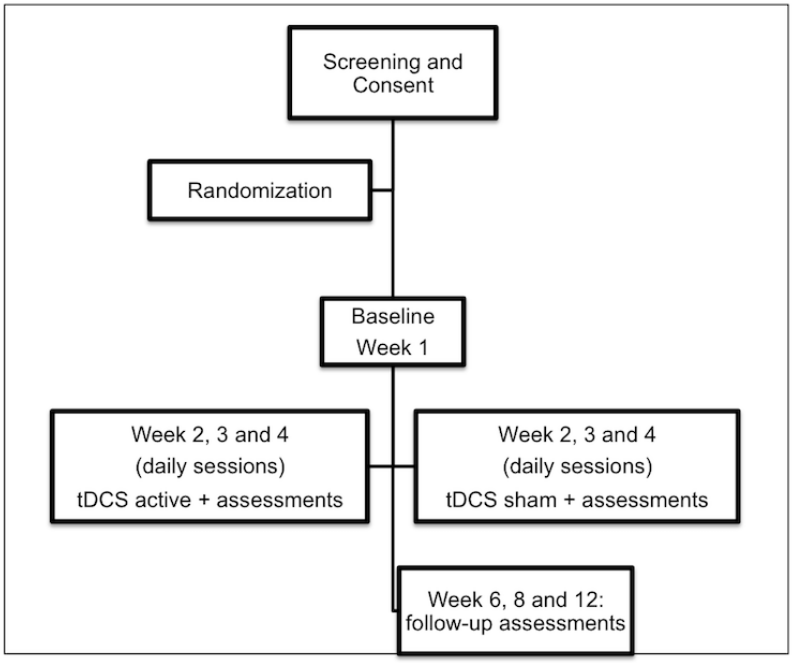
Intervention

The treatment will be administered for 3 weeks with intervention sessions daily from Monday to Friday for a total of 15 days of electrical stimulation [37]. The participants will not receive cash, reimbursements, food, transportation, or any compensation for their participation in the trial. After the initial assessment and before randomization, the subjects will be informed about the possible sensations with the stimulation and instructed not to reveal the sensation experienced.

Participants will be seated comfortably in an armchair while receiving tDCS. All subjects will receive 20 minutes of either sham or active tDCS, using a pair of 35 cm^2 surface sponge electrodes soaked with physiologic saline and fixed to the head with elastic bands. The transcranial stimulation will be applied by a constant current device (Soterix 1×1 Low-Intensity Stimulator, Soterix Medical Inc) with an intensity of 2 mA. A gradual current ramp-up and ramp-down with 30-second durations will be used. The anode will be placed over C3/C4 (International 10-20 electroencephalogram system), which corresponds approximately to the location of M1 of the contralateral side to the most affected knee. The cathode electrode will be placed over the contralateral orbital, meaning ipsilateral to the most affected knee. The tDCS will be administered by a physician with specific training is this modality of intervention.

Sham tDCS stimulation will look and feel exactly the same as the active stimulation; however, the stimulator will deliver 2 mA of current for only 30 seconds. This sham stimulation method is frequently used and has been shown to be reliable [42].

Figure 1. Flowchart of the study based on Consolidated Standards of Reporting Trials criteria. tDCS: transcranial direct current stimulation.



Outcome Measurements

Following determination of participant eligibility and obtaining informed consent, we will collect baseline information about the subjects through a structured interview. Collected data will include sociodemographic information, mood and cognitive evaluation, radiographic data, and clinical history. We will perform all assessments during the baseline visit to obtain data to compare with the follow-up visits. Baseline data will be collected 1 week prior to the beginning of treatment. After 3 weeks of intervention, we will evaluate the participants over the course of 2 months, with 3 follow-up visits during this period (see Figure 1 for flow diagram). These outcome time points were chosen based on tDCS trials to assess early and late effects [27,36,37].

Primary Outcome

We will analyze pain intensity in the previous 24 hours using the Brief Pain Inventory (BPI); this is a short, self-report questionnaire [43]. The BPI includes 4 items that measure pain intensity (pain right now, pain on average in last 24 hours, worst pain in last 24 hours, and least pain in last 24 hours) using an NRS from 0 (no pain) to 10 (pain as bad as you can imagine). The mean of these 4 pain items will be used as our primary outcome. The BPI also includes 7 items that assess the impact of the pain on functioning using a 0 (no interference) to 10 (complete interference) rating scale, which will be used as a secondary outcome.

Secondary Outcomes

Quality of Life

We will assess health-related quality of life using the 12-Item Short Form Health Survey questionnaire, which comprises 8 domains that include physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social functioning, emotional role functioning, and mental health [44].

Pain Perception

Mechanical detection threshold (MDT) will be assessed using a Von Frey monofilament (VFM) as a mechanical stimulating device to evaluate light touch and pinprick sensation in small cutaneous regions. The investigator will use the smallest weighted monofilament, followed by sequentially larger monofilaments until the participant reports when the light touch sensation is first detected and then until the pinprick sensation is detected. VFM will be applied perpendicular to the skin with the correct amount of force to bow the monofilament for approximately 1.5 seconds. VFM will be applied first to the thenar region, ipsilateral to the most affected knee, and then applied to the most painful knee [45].

Mechanical pain threshold (MPT) will be measured using the same technique used to assess the MDT. However, the subject will be asked to report the smallest monofilament that produces pain. Following this, we will apply the same monofilament on either region 3 times, and the participants will be asked to rate the pain using an NRS; the mean score will then be calculated [45,46].

Pressure Pain Threshold

The pressure pain threshold (PPT) will be assessed using a pressure algometer (Commander Echo Algometer, JTECH Medical Industries Inc) that has a 1-cm^2 rubber probe. The probe will be applied perpendicular to the skin until the subject first reports that the pressure sensation changes to a pain sensation. Participants will be asked to rate the pain using an NRS. The pressure will be applied to exactly the same regions that we will use to assess MDT and MPT [47].

Conditioned Pain Modulation

CPM will be measured using cold water as the conditioned stimulus and pressure as the test stimulus to assess endogenous pain modulation. Pressure will be applied using the same device and technique as for the PPT. Participants will be asked to immerse their contralateral hand to the most affected knee in a cold water bath maintained at 10°C for approximately 1 minute. In the last 30 seconds, the test stimulus will be applied following the PPT procedure [15-17].

We will calculate the percentage change in pain scores following CPM, a measurement we will call CPM-P, and the change in the PPT after the CPM that we will call CPM-PPT. Both of them will be calculated using the following formula: (post-CPM trial score − pre-CPM trial score / pre-CPM trial score) × 100. For CPM-P, a negative score will indicate pain inhibition after the conditioning stimulus. For CPM-PPT, a positive score will indicate pain inhibition after the conditioning stimulus.

Physical Functioning

The Western Ontario and McMaster Universities Osteoarthritis Index is a valid and reliable instrument commonly used to assess pain and disability in studies of knee OA. The questionnaire includes 3 subscales to assess pain, perceived disability, and joint stiffness. The total score ranges from 0 to 96, with higher values indicating greater physical impairment [48].

The Lequesne Algofunctional Index is a questionnaire that assesses 3 components of severity of OA: pain, maximum walking distance, and activities of daily living. The total score ranges from 0 to 24, with higher values indicating greater physical impairment [49].

The timed up and go test is a reliable and practical test to evaluate functional capacity commonly used in research studying elderly populations, especially because of its capacity to assess risk of falls and gait function. Subjects will be asked to get up from a chair in which they were fully supported, walk 3 meters, turn around, return by the same route, and sit back down on the chair with their back supported. We will measure the time required to complete the test. The test will be performed twice, and the lowest score will be recorded [50-52].

The one leg stance test is used to evaluate postural balance. The participants will be asked to stand unsupported on one foot while looking straight ahead with their hands on hips. We will measure the time the subject is able to maintain balance until the contralateral foot touches the ground. The test will be performed twice, and the highest score will be recorded [52,53].

Pain Impact on Functioning

The mean of the 7 BPI interference items (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life) will be used to assess the pain impact on functioning.

Patient Global Assessment

We will analyze the patient's global assessment on how the intervention affects the patient's status using a 0-100 visual analog scale (VAS) scale [54].

Adverse Effects

At each stimulation session and at all follow-ups, participants will be administered a questionnaire to evaluate potential adverse effects of stimulation on a 5-point scale. The main potential adverse effects include headache, neck and scalp pain, tingling, sleepiness, and acute mood change. If any side effect is reported, its potential relationship with the intervention will be assessed [55].

To assess the safety of tDCS, we will analyze the mood and cognition of the subjects at each stimulation session and at all follow-ups. Mood will be assessed with a 0-100 VAS scale by asking the subject to rate their own emotions including anxiety, depression, stress, and sleepiness. Cognition will be analyzed using the Mini-Mental State Examination, a brief screening of cognitive abilities [56].

Sample Size and Data Analysis

The sample size was estimated using the minimal clinically important difference (20% reduction from the baseline) in the outcome of pain intensity measured by the NRS as a parameter. The effect size and the probability of error type I (alpha) and type II (beta) were 0.59, .05, and .2, respectively. According to the sample calculation, that total size would be 94 participants. We will increase the sample size by 10% to account for dropouts and other unexpected factors. Thus, the final sample size is 104 subjects.

All analyses will be conducted according to the principle of intention-to-treat (ITT) using a regression-based single imputation method. The ITT population will include all randomized subjects. We will perform an additional sensitivity analysis in which we will use the method of multiple imputation. Initially, the baseline characteristics between sham and tDCS groups will be tested using Student *t* tests; to analyze our primary outcome, which is pain intensity measured by BPI, we will adopt a mixed analysis of variance model in which the dependent variable will be the outcome (BPI) and the independent variables will be group (tDCS-a or tDCS-s), time (baseline and after treatment and follow-up), and the interaction group time. Secondary analyses will be conducted in an exploratory manner (no correction for multiple comparisons). Similar analysis will be conducted for the adverse effects measuring continuous outcomes, and for the categorical outcomes, we will use Fisher exact tests. In both cases, for the safety analysis, we will use uncorrected *P* values to increase the likelihood of detecting detrimental adverse effects.

Results

This clinical trial began enrollment in April 2018. As of publication, 40 subjects have been evaluated, 25 have been included satisfactorily, and 10 participants have completed the entire protocol. We estimate enrollment will be completed within 2 years. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications will be authorized by the study investigators.

Discussion

This study will assess a relevant public health problem, as the overall population is getting older and the prevalence of chronic disorders is increasing. This randomized clinical trial will evaluate the effects of the cumulative noninvasive brain stimulation technique as an instrument to decrease pain intensity by inducing neuroplasticity in brain circuits related to central sensitization. As a secondary effect, we will observe impact on the quality of life and mobility performance in elderly patients with knee OA.

This trial will contribute to understanding the underlying mechanisms of the analgesic effects of tDCS over the motor cortex by assessing the CPM response of the subjects. In this trial, we are only enrolling subjects with defective endogenous inhibitory pain system. We chose this criteria given the mechanisms of tDCS, as well as effects of tDCS on this system [57-58]. Therefore, this study will be important to preliminarily test the suitability of CPM as a valuable prognostic and surrogate marker. Finding better neurophysiological markers for the use of tDCS is critical to advance this field. A potential significant correlation between pain scores and CPM response will indicate that CPM may be a useful marker.

Most interventions for OA do not target the central sensitization and defective descending inhibitory pain system. For instance, nonsteroidal anti-inflammatory drugs inhibit the two recognized forms of prostaglandin synthase, thus providing an analgesic and anti-inflammatory effect; however, their prolonged use is limited because they carry risk for cardiovascular and upper gastrointestinal diseases [59,60]. Thus, tDCS can be important for nonresponders to the traditional treatment. This intervention has the opposite effect on the endogenous pain system when compared to opioids, which, when used chronically, may increase sensitivity to a noxious stimulus and consequently induce hyperalgesia [61].

Another important finding from this trial concerns the additional data we will provide on the tDCS effects in elderly populations. While there have been a fair number of trials testing tDCS in chronic pain, there have been few randomized clinical trials testing tDCS for chronic pain in elderly patients. To date, there have been no well-powered trials (such as this one with 104 subjects) designed to test a homogenous population [29,62,63]. We believe that this trial can provide important information to advance this therapy in this population.

We decided to use 15 stimulation sessions based on a recent trial on chronic pain due to fibromyalgia, which estimated 15 tDCS sessions as the median number of stimulations to produce clinically meaningful outcomes [37].

The safety of tDCS has been well established, and after several studies, researchers concluded that tDCS induces only temporary mild effects. The most common side effects include headache, dizziness, nausea, mild pain, itchy sensation, and skin redness under area of the electrodes [26,38,55-57]. However, it is important to assess safety in elderly patients given that there is much less experience with this population. This trial will provide additional data for this domain, which will be useful when planning future trials.

Some concerns about the study should be discussed. One of the possible issues may be the combination with other therapies, which may influence the results. Given the relatively large sample size of subjects, we believe that this potential covariate will be balanced in the two groups. In addition, subjects will be asked to remain stable in their drug treatment, and any changes will be noted for secondary subgroup analysis. Finally, although blinding is not perfect in tDCS and 10% to 20% may become unblinded, we have demonstrated in longitudinal trials that there are no blinding-related biases in a tDCS clinical trial for a parallel design [64]. This trial has several strengths, such as a relatively large sample (one of the largest in tDCS pain research) and a population selected based on the endogenous mechanisms of tDCS (CPM).

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Conflicts of Interest

None declared.

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Abbreviations

BPI: Brief Pain Inventory
CPM: conditioned pain modulation
CPM-P: percentage change in pain score following conditioned pain modulation
CPM-PPT: change in pressure pain threshold after conditioned pain modulation
CONSORT: Consolidated Standards of Reporting Trials
HSP: Sao Paulo Hospital
ITT: intention-to-treat
M1: primary motor cortex
MDT: mechanical detection threshold
MPT: mechanical pain threshold
NRS: numeric rating scale

OA: osteoarthritis
PPT: pressure pain threshold
tDCS: transcranial direct current stimulation
tDCS-a: active transcranial direct current stimulation
tDCS-s: sham transcranial direct current stimulation
VAS: visual analog scale
VFM: Von Frey monofilament

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Protocol

Early Detection of Cardiovascular Changes After Radiotherapy for Breast Cancer: Protocol for a European Multicenter Prospective Cohort Study (MEDIRAD EARLY HEART Study)

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Abstract

Background: Breast cancer is the most common cancer among women, and radiotherapy plays a major role in its treatment. However, breast cancer radiotherapy can lead to incidental irradiation of the heart, resulting in an increased risk for a variety of heart diseases arising many years after radiotherapy. Therefore, identifying breast cancer patients at the highest risk for radiation-induced cardiac complications is crucial for developing strategies for primary and secondary prevention, which may

contribute to healthy aging. There is still a need for precise knowledge on the relationship between radiation dose to specific cardiac structures and early subclinical cardiac changes and their occurrence over time that could finally lead to cardiac complications.

Objective: The MEDIRAD EARLY HEART study aims to identify and validate new cardiac imaging and circulating biomarkers of radiation-induced cardiovascular changes arising within first 2 years of breast cancer radiotherapy and to develop risk models integrating these biomarkers combined with precise dose metrics of cardiac structures based on three-dimensional dosimetry.

Methods: The EARLY HEART study is a multicenter, prospective cohort study in which 250 women treated for breast cancer and followed for 2 years after radiotherapy will be included. Women treated with radiotherapy without chemotherapy for a unilateral breast cancer and aged 40-75 years meet the inclusion criteria. Baseline and follow-up data include cardiac measurements based on two-dimensional speckle-tracking echocardiography, computed tomography coronary angiography, cardiac magnetic resonance imaging, and a wide panel of circulating biomarkers of cardiac injury. The absorbed dose will be evaluated globally for the heart and different substructures. Furthermore, the dose-response relationship will allow modeling the radiation-induced occurrence and evolution of subclinical cardiac lesions and biomarkers to develop prediction models.

Results: This study details the protocol of the MEDIRAD EARLY HEART study and presents the main limits and advantages of this international project. The inclusion of patients began in 2017. Preliminary results are expected to be published in 2019, and complete analysis should be published in 2021.

Conclusions: The MEDIRAD EARLY HEART study will allow identifying the main cardiac imaging and blood-based determinants of radiation-induced cardiac injuries to better propose primary and secondary preventive measures in order to contribute to enhanced patient care and quality of life.

Trial Registration: ClinicalTrials.gov NCT03297346; https://clinicaltrials.gov/ct2/show/NCT03297346 (Archived by WebCite at http://www.webcitation.org/72KS7MIUU)

Registered Report Identifier: RR1-10.2196/9906

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KEYWORDS

biomarkers; breast cancer; cardiotoxicity; cardiac diagnostic imaging; radiotherapy; radiation dosimetry

Introduction

Cancer is a major burden on society, which is expected to increase worldwide due to the growth and aging of the population. Furthermore, breast cancer (BC) is the most commonly diagnosed cancer among women. In 2016, BC accounted for 29% of the total new cancer cases and 14% of the total cancer-related deaths among women worldwide [1]. While its incidence has been increasing in the past decade, the prognosis has markedly improved over the last decades with enhanced screening and medical support for these patients, resulting in longer life expectancy and 5-year relative survival rate > 60%-95% according to the age class in most Western countries [2]. This is due to improved detection programs and treatment modalities, including improved radiotherapy (RT) techniques. In the past few decades, RT has been increasingly used for the treatment of BC. Research has shown that RT presents a benefit in terms of reducing local recurrence and deaths resulting from BC [3]. Due to this increased survival rate, the interest in potential adverse effects and long-term consequences related to RT has spiked.

RT plays a major role in the treatment of BC, as >60% of all BC patients are irradiated as part of their curative treatment, and it improves outcome in terms of reducing the local recurrence and deaths resulting from BC [4]. However, BC RT can lead to incidental irradiation of the heart due to its presence within the irradiation field, resulting in an increased risk for a variety of heart diseases arising many years after RT [5], such as ischemic heart disease, congestive heart failure, arrhythmias, conduction defects, valvular disease, or pericarditis, with relative risks within the range of 1.2-3.5 on comparing patients with left-sided BC (corresponding to patients with higher exposure to the heart) to patients with right-sided BC [6-8]. In parallel with the increase in the incidence of BC, the prevalence of BC survivors at risk for cardiac complications will, thus, gradually increase [3,4,6-8]. Technological developments in RT over the last decades, such as intensity-modulated radiotherapy or volumetric modulated arc therapy and deep inspiration breath-hold, have allowed for a marked reduction of cardiac doses, in particular for patients with left-sided BC; the mean heart dose has decreased from >5 Gy in the 1950s to <3 Gy in the last decade [9]. It has been shown that the use of these techniques in BC patients is of concern to the radiation oncologists and is widely implemented [10,11]. However, cardiac damage has been shown to be correlated with the mean heart dose, with a 7.4% increase in the rate of acute coronary events per 1 Gy (95% CI 2.9-14.5; P<.001), with no minimum threshold for risk [8]. The risk for acute coronary events within first 9 years of RT has recently been confirmed by an additional publication [12], showing marked relationship between cardiac radiation dose and acute coronary event incidence. Therefore, as there appears to be no threshold dose below which cardiac complications do not appear, radiation-induced cardiac diseases remain potential, severe, late complications of BC RT. Moreover, dose distributions in the heart are extremely heterogeneous, and some cardiac substructures such as the apex and the apical-anterior segment can still receive higher doses. Therefore, there is still an urgent need for preventive measures. Long before the onset of clinically significant late cardiac

complications, subclinical cardiac changes may occur over weeks, months, or years after RT that can be detected using anatomical and functional cardiac imaging or circulating biomarkers [13].

In the context of BC RT-induced functional cardiac changes, a recent advanced echocardiographic technique (automated two-dimensional speckle-tracking echocardiography, ECHO-ST, or cardiac strain] has been used for detecting and quantifying subtle (subclinical) disturbances in left ventricular strain and function. A Belgian team first showed that global longitudinal strain and strain rate were substantially decreased (mean 5%) during the first year following breast RT [14]. This result was confirmed by other studies in patients with left-sided BC whose global longitudinal strain and apical strain were diminished. In addition, the basal regions showed a compensatory increase in function, although not sufficient to compensate for the global functional loss resulting in a decrease in the global longitudinal strain [14-18]. Moreover, among patients with right-sided BC RT, a deterioration in basal anterior strain segments after RT was observed, whereas the global function remained unaffected [19].

Cardiac computed tomography (CT) without contrast and CT coronary angiography (CTCA) allows the determination of the coronary artery calcium (CAC) score and detection of plaques and stenosis along the coronary arteries. The presence and diffusion of calcium, plaque, and stenosis expose patients to a higher risk for coronary artery disease (CAD). Based on an analysis of 15 segments of coronary arteries per patient with acute chest pain, an increase in calcified and noncalcified plaques of around 15% was observed during a 2-year follow-up [20]. While this study did not consider radiation exposure of the heart, it does illustrate that the CTCA could be used for monitoring short-term coronary changes and has the potential to detect the onset or progression of early coronary changes due to irradiation among women treated with BC RT. To date, three studies have measured the amount of CAC in the years following RT treatment for BC. In two studies, no elevated CAC scores in BC patients were found 5-15.7 years after RT treatment, whereas one study did find an increase in the CAC score depending on the radiation dose to the heart [21-23]. Among the studies that did not find a CAC score increase, one did not include baseline CAC scores and the other only included a relatively small number of patients, making it difficult to draw definitive conclusions from these two studies. In young Hodgkin's lymphoma survivors (all aged <55 years), elevated CAC scores have been found 5-35 years after RT [24-26]. A study concerning the general population investigated CAC scores at baseline and after 10 years of follow-up [27]; the results showed that the diagnosis of cancer and its treatments were markedly associated with an increase in CAC scores even after accounting for cardiac risk factors. The results of these studies suggest that RT is associated with increased CAC scores in the long term and, therefore, support the hypothesis that accelerated atherosclerosis is one of the mechanisms contributing to an increase in RT-induced cardiac events after cardiac irradiation.

Cardiac magnetic resonance imaging (MRI), which is considered as the gold standard to characterize myocardial tissue and measure ventricular volumes and function, was used to show that right ventricular systolic function was decreased in a BC cohort at 24 months after RT [16]. Furthermore, a decline in temporary ejection fraction was observed on MRI (in patients treated with three-dimensional [3D] conformal radiotherapy and not in patients treated with intensity-modulated radiotherapy) at 6 months, which resolved at 24 months. Left and right ventricular systolic functions determined using MRI were reduced at 24 months (but still within the normal range) for the whole cohort. Furthermore, using T1 mapping, a promising technique to quantify morphologic tissue injuries, it was shown in cancer survivors (including BC patients) that interstitial or diffuse myocardial fibrosis was elevated 3 years after anthracycline-based chemotherapy independent of the underlying cancer or comorbidities, suggesting that imaging biomarkers of interstitial fibrosis are related to prior receipt of potentially cardiotoxic cancer treatment [28], which may also include ionizing radiation.

A major challenge is the identification of reliable circulating biomarkers that could help diagnose and predict cardiotoxicity. Many classical biomarkers (eg, C-reactive protein, N-terminal pro-B-type natriuretic peptide, and troponin) have been shown to be potential biomarkers for cardiac damage after RT [29]. In addition, circulating inflammatory cytokines indicated tissue inflammation [30]. Radiation injury to the myocardium is primarily caused by damage to the microvasculature, leading to inflammatory and thrombotic changes, capillary loss, focal ischemia, and interstitial fibrosis [31,32]; these pathological changes can cause congestive heart failure.

One relatively recent advancement in this area is the discovery of circulating extracellular vesicles (EVs), including microparticles and exosomes, and their emergence as mediators of a new important mechanism of cell-to-cell communication [33]. The role of EVs in mediating vascular dysfunction suggests that they may represent novel pathways in short- or long-distance paracrine intercellular signaling in the vascular environment. High levels of circulating EVs (involving microparticles) found in many cardiovascular diseases demonstrate the importance of platelet, monocyte, and endothelial activation and could condition remote sustainability illnesses [34].

Exosomes carry a composite cargo of cardiac microRNAs (miRNAs). MiRNAs are posttranscriptional inhibitory regulators of gene expression that are emerging as important mediators of intercellular communication, being involved in the transmission of biological signals between cells. To date, several miRNAs have been identified as having a primary impact on many biological processes that are of direct relevance to cardiovascular complications. The exosomal trafficking of miRNAs from the heart is largely unexplored. Interventional cardiologists have already provided evidence that cardiac-expressed miRNAs (miR-1, miR-133a, miR-133b, miR-208a, miR-208b, and miR-499) increase in the blood acutely following a myocardial infarction, and some of these studies have additionally scrutinized the diagnostic potential of miRNAs by comparing them with cardiac troponin [35,36]. In a clinical study, it has been demonstrated that the plasma concentration of EVs and their cargo of cardiac miRNAs increased in patients undergoing

coronary artery bypass graft and were positively correlated with cardiac troponin [36]. Another hypothesis that remains to be explored is that the irradiation may be responsible for an increase in the number of circulating levels of EVs associated with certain miRNAs expressed by the cells of the heart tissue. Finally, studies have examined the global DNA methylation and risk for cardiovascular disease. The methylation of Bcl-2/adenovirus E1B 19kD-interacting protein 3, SuperOxyde Dismutase, Glutathione S-transferase P, Apolipoprotein E, B-cell lymphoma 2, BCL-2-associated X protein, and tissue inhibitor of metalloproteinases-3 promoters has been associated with the presence of CAD, which is the most prevalent cardiovascular disease following the exposure to radiation and may be useful for diagnostic and monitoring purposes [37].

These previous studies have shown that early subclinical cardiac changes can occur in BC patients after RT. Additionally, classical cardiac biomarkers have been shown to be potential candidates to monitor cardiac damage after RT. Identifying the main cardiac imaging and blood-based determinants of radiation-induced cardiac injuries is crucial for developing strategies for primary and secondary prevention. Primary prevention includes radiation dose optimization to the most critical structures of the heart. Secondary prevention requires identification of patients at risk as early as possible before and after RT. So far, little has been done regarding the relationship between dose distribution to different anatomical cardiac structures during RT and early cardiovascular changes that may lead to cardiac complications. Mathematical models have been developed in recent years with the aim of using dosimetric data to estimate a complication probability—the Normal Tissue Complication Probability (NTCP) models. Research on parameters to optimize the NTCP models (physical imaging, dosimetry, and clinical) is a major challenge to improve knowledge on the relationship between a received dose and toxicity to healthy tissue [38,39]. Moreover, the enrichment of these models with biological data is fundamental to improve risk prediction. Primary and secondary prevention measures require precise knowledge of the relationship between the dose to specific cardiac structures and the occurrence of early subclinical cardiac changes over time. To date, little has been done on elucidating the specific relationships between doses to cardiac structures and subsequent early cardiac toxicity, and NTCP models have been poorly exploited [40]. However, a prerequisite for further sparing of tissue subregions, as well as the analysis of NTCP properties, requires prospective identification of these structures, and their dose-volume properties must be taken into account in prospective treatment planning [41].

In this context, in the frame of the European MEDIRAD project [42], the EARLY HEART study was launched in July 2017 with the aims of identifying and validating the most important cardiac imaging biomarkers (based on ECHO-ST, CTCA, and MRI) and circulating biomarkers of radiation-induced cardiovascular changes arising within first 2 years of BC RT and of developing risk prediction models, such as NTCP models, integrating these biomarkers combined with precise dose metrics of cardiac structures based on 3D-dosimetry.

Methods

Study Design

MEDIRAD EARLY HEART (NCT03297346) is a multicenter, prospective cohort study that will include female patients with left- and right-sided BC treated with postoperative RT without chemotherapy after primary breast-conserving surgery. The patients will be followed for 2 years after RT, based on cardiac imaging and circulating biomarkers further detailed below. Five investigating centers are involved in the study: Clinique Pasteur (Toulouse, France) for the Institute of Radiation Protection and Nuclear Safety (Fontenay-aux-Roses, France), the University Medical Center Groningen (UMCG; Groningen, the Netherlands), die Klinikum rechts der Isar der Technischen Universität München (TUM MED; Munich, Germany), Institut Català d'Oncologia (Girona, Spain), and Centro Cardiovascular da Universidade de Lisboa (Lisbon, Portugal). Furthermore, Paris Descartes University (Paris, France) is involved in the study as core lab for the centralized analysis of cardiac CT and cardiac MRI. Data collection is expected to be performed until autumn 2020.

Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki (amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the principles of "Good Clinical Practice" and the Medical Research Involving Human Subjects Act (WMO). The 5 investigating centers have received approvals from their local ethical committees (France: Comité de Protection de Personnes Sud-Ouest IV, ID: CPP2015/66/2015-A00990-69–R1, and Agence Nationale de Sécurité des Médicaments, ID: 150873B-12; the Netherlands: Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen [METc UMCG], ID: METc 2017/379, NL62360.042.17; Germany: Ethikkomission der Technischen Universität München, ID: 235/17 S; Spain: Comitè d'Etica d'Investigatio CEAi GIRONA, ID: EARLY HEART v1.1 05/07/2017 i FIP v1.3; Portugal: Comissao de Ética do Centro Hospitalar Lisboa Norte e do Centro Académico de Medicina de Lisboa [CHLN e CAML], ID: 257/2017).

Study Population, Site Participation, and Recruitment

In this study, we plan to include 250 female patients with unilateral BC treated at the 5 participating centers with postoperative modern photon-based planning CT after breast-conserving surgery, without chemotherapy, who are aged 40-75 years at the time of RT. The determination of the size of the study population is based on power calculation detailed later.

Textbox 1 details the additional inclusion and exclusion criteria as well as early dismissal (after inclusion) criteria. Each patient is included at the baseline before RT and followed for 2 years after RT. Informed consent of each patient was collected before inclusion.

Textbox 1. Inclusion, exclusion, and early dismissal criteria in the EARLY HEART study.

Inclusion criteria

- Female unilateral breast cancer patients
- Treated with primary breast-conserving surgery for stage I-III invasive adenocarcinoma of the breast or ductal carcinoma *in situ*
- Age 40-75 years at the time of starting radiotherapy
- World Health Organization performance status 0-1
- Planned for radiotherapy alone to the breast with or without the lymph node areas
- Radiotherapy based on planning-computed tomography using either three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or volumetric modulated arc therapy/RapidArc
- Written informed consent

Exclusion criteria

- Male breast cancer patients
- Neoadjuvant or adjuvant chemotherapy
- M1 disease (metastatic breast cancer)
- Medical history of coronary artery disease and myocardial infarction and atrial fibrillation
- Previous thoracic or mediastinal radiation
- Contraindications to injection of iodinated contrast such as allergy or renal failure
- Pregnancy or lactation

Dismissal criteria

- Atrial fibrillation detected on electrocardiogram before radiotherapy
- Abnormal echocardiography before radiotherapy defined as either left ventricular ejection fraction <50% or longitudinal strain ≤−16% or longitudinal strain rate <−1% or abnormal wall motion
- Computed tomography coronary angiography results before radiotherapy requiring revascularization
- Presence of myocardial infarction based on magnetic resonance imaging before radiotherapy

Conduct of the Study

Before Inclusion

At each center, radiation oncologists enable first contact with women diagnosed with BC. During the first visit with the radiation oncologist, he or she presents the study and its implications to female patients for whom RT is planned. The radiation oncologist ensures that women meet the inclusion criteria in the study and study information leaflet detailing the protocol is given with a consent form.

Before Start of Radiotherapy

About 1-2 weeks before the start of RT, women agreeing to participate in the study hand their signed written informed consent form and are then considered as included. Once included, the women's follow-up protocol is implemented. Before the start of RT, several interventions are performed.

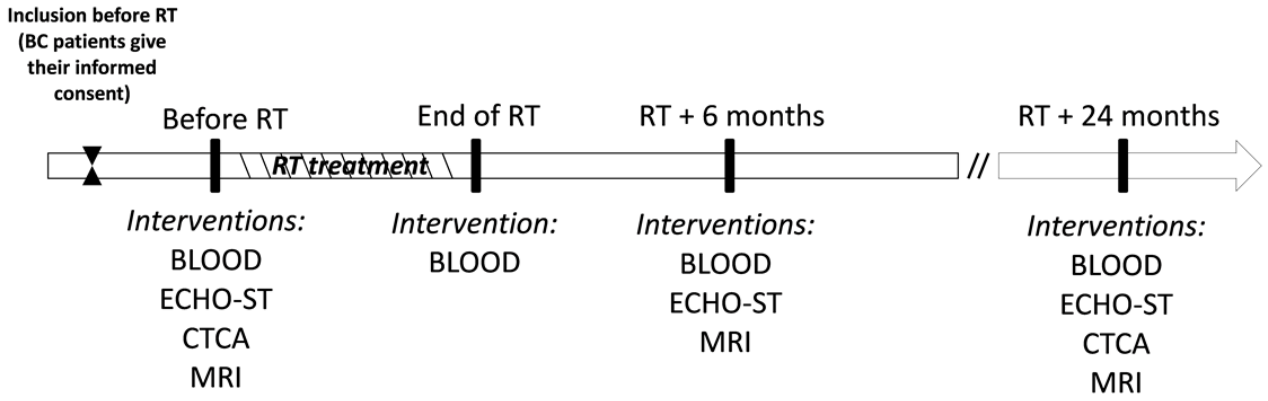
- An electrocardiogram to detect any arrhythmia, followed by an automated ECHO-ST, which is the most commonly used modality to evaluate myocardial dysfunction and a new technique for assessing myocardial deformation.
- CTCA using both low-dose, nonenhanced and enhanced CT scans to evaluate coronary artery lesions by assessing morphological information, including plaques and stenosis of the arteries, and determination of the CAC score.
- MRI to measure the ventricular function and size and wall thickness of the two heart chambers; tissue characterization by delayed enhancement; and pre- or postcontrast T1 mapping and precontrast T2 mapping of the left ventricle.
- Blood sampling (BLOOD) will be performed to allow analyses of circulating biomarkers based on a panel of circulating classical and novel blood-based biomarkers (further details below).

Furthermore, toxicity is assessed according to the Common Terminology Criteria for Adverse Events (version 4.03), which is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer therapy clinical trials and other oncology settings.

Subsequent Follow-Up

During subsequent follow-up, imaging and circulating biomarkers are collected at specific time points after RT up to 24 months: (1) at the end of RT: BLOOD; (2) 6 months after RT: ECHO-ST, MRI, and BLOOD; (3) 2 years after RT: electrocardiogram and ECHO-ST, CTCA, MRI, and BLOOD. Figure 1 describes the different steps of the EARLY HEART study protocol.

Figure 1. Main steps of the EARLY HEART study protocol. RT: radiotherapy; BC: breast cancer; BLOOD: blood sample for circulating biomarkers; ECHO-ST: two-dimensional speckle-tracking echocardiography; CTCA: computed tomography coronary angiography; MRI: magnetic resonance imaging.



Data Collection

A precise description of the cancer and information about main risk factors of a cardiac event (eg, age, body mass index [BMI], smoking status, blood pressure, hypertension, diabetes, hypercholesterolemia, etc) are collected at inclusion. In addition, we collect information on the use of hormonotherapy, such as antiaromatase, as it may lead to an increased cardiovascular risk [43,44]. Cardiac imaging (ECHO-ST, CT, and MRI) and circulating biomarkers measurements are detailed in Textbox 2 and Figures 1 and 2. Strain measurements will be based on automated ECHO-ST, which partly depends on the type of device (eg, GE, Philips, and Siemens). Not all the centers use the same device, but each patient from each center will be followed using the same device; this will allow comparing the evolution of strain measurements from baseline to the end of follow-up as a relative value, without been biased by the type of device [45].

Dosimetry

For cardiac dosimetry, automated segmentation of all cardiac structures (including coronary arteries) is performed to ensure the uniformity of the segmentation procedure across centers. This multiatlas automatic segmentation tool of the heart, developed by UMCG, is based on the atlas by Feng et al [48] (Mirada RTx [version 1.6]; Mirada Medical, Oxford, United Kingdom) [49]. This automatic segmentation allows reducing the interobserver variability in contouring organs at risk. With delineated volumes, it is possible to calculate the exact planned radiation dose for the different volumes of the heart. Using the individual doses of patients, the dose-effect relationship can be calculated independently of RT technique or treatment volume. For the cardiac structures such as the whole heart, left atrium, right atrium, left ventricle, right ventricle, strain segments of the left ventricle, and coronary arteries, a minimum dose (D_{min}) is obtained, as well as a maximum dose (D_{max}), a mean dose (D_{mean}), volumes of the structure receiving at least 1, 2, up to the total dose of Gy (V_1, V_2,...until the $V_{total\ dose}$). The same is obtained for the D_1, D_2, and so on, up to D_{100} (the dose to 1%, 2%, up to the total of 100% of the volume).

Study Endpoints

Primary Endpoint

The primary endpoint is a mean decrease in the global longitudinal strain or global longitudinal strain rate, determined using cardiac ECHO-ST, of at least 2.5% between the baseline and 24 months after RT [50,51].

Secondary Endpoints

Secondary endpoints are defined as follows:

- Changes in myocardial function compared with baseline assessed using echocardiography 6-24 months after RT.
- Anatomical changes in coronary artery atherosclerosis compared with baseline (number of coronary segments containing any plaque or stenosis and calcium score) on CTCA 24 months after RT. The endpoint is defined as ≥15% changes.
- Myocardial changes (morphology, function, tissue characterization by the delayed enhancement, and pre- or postcontrast T1 mapping) compared with baseline on MRI 6-24 months after RT. The endpoint is an increase in the mean precontrast T1 mapping value of, at least, 7%.
- Temporal changes in circulating biomarkers at the end of RT and 6-24 months after RT compared with baseline. The endpoint is a statistically significant increase or decrease in each biomarker between time points.

Statistical Analysis

Sample Size Calculation

The MEDIRAD EARLY HEART study includes 250 women. With 250 patients, this study will have a statistical power of 80% to detect a minimum decrease of 2.5% in global longitudinal strain between baseline measurement and 24 months after RT measurement [14]. The baseline value was derived from the literature: mean global longitudinal strain before RT = −16.5% (SD 2.1%) [52]. In addition, an alpha level of 5% was considered, based on paired tests for comparison with the baseline reference value. Furthermore, the final size was slightly increased to consider the possible loss to follow-up due to death or other reason.

Textbox 2. Main cardiac imaging and circulating biomarkers in the EARLY HEART study.

Two-dimensional speckle-tracking echocardiography

- Global and segmental longitudinal strain and strain rate (more details on the definition of segments in Figure 2 [46])
- Global and segmental radial strain and strain rate
- Left ventricular ejection fraction using Simpson's biplane method
- E/A wave ratio: ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)
- E/Ea wave ratio: ratio of peak velocity blood flow from gravity in early diastole (the E wave) to Early diastolic velocity of lateral mitral annulus (e' lateral)
- Tricuspid annular plane systolic excursion
- Heart rate
- Cardiac output measured by multiplying heart rate by the stroke volume

Computed tomography coronary angiography

- Coronary artery calcium score, based on Agatston, volume, and mass; overall and per artery (left main coronary artery, left anterior descending artery, left circumflex artery, and right coronary artery)
- Presence and type of plaque (noncalcified, partly calcified, and calcified); overall and per segment or artery (more details in Figure 3 [47])
- Presence and severity of luminal narrowing based on plaque; overall and per segment or artery

Magnetic resonance imaging

- Cardiac morphology: right ventricular end-diastolic and end-systolic volumes, left ventricular end-diastolic and end-systolic volumes, left ventricular mass, etc
- Cardiac function: left ventricular ejection fraction, right ventricular ejection fraction
- Presence and extent of myocardial infarction based on delayed enhancement
- Tissue characterization based on pre- or postcontrast T1 mapping
- Presence of myocardial edema based on T2 mapping

Circulating biomarkers

- Classical markers:
  - Markers of cardiac injury: C-reactive protein, Troponin I, Troponin T, B-type natriuretic peptide (BNP), N-terminal-proBNP, beta2-microglobulin, Galectin 3
- New biomarkers:
  - Extracellular vesicles: microparticles: CD14 (monocytes), CD31 (endothelial), CD41 (platelets), CD3 (lymphocytes), CD235a (erythrocytes); exosomes
  - MicroRNAs (miRNAs): cardiac miRNAs (miR-1, miR-24, miR-133a/b, miR-208a/b, miR-210); noncardiovascular miRNAs (miR-122)
  - Circulating DNA methylation

Planned Analysis

Differences in biomarkers between unexposed and paired exposed groups (eg, right- vs left-sided breast RT) at different time points will be analyzed to generate preliminary hypotheses on the effects of RT on the heart. To investigate the time course of continuous variables extracted from ECHO-ST, CTCA, or MRI measurements and the relation with radiation dose to a variety of cardiac structures, mixed regression models will be used. Confounding variables such as age, blood pressure, BMI, smoking status, hypertension, hypercholesterolemia, or use of hormonotherapy will be included in the risk models. Changes in cardiac biomarkers will be correlated with dose distribution data. An integrative clinical-biological risk score will be developed for individual risk prediction and, finally, multivariable NTCP models will be constructed integrating these biomarkers combined with dose metrics of cardiac structures based on 3D-dosimetry.

All statistical analyses will be performed using SAS statistical software for Windows (SAS Institute, Cary, NC). Furthermore, linear regression models will be performed using generalized estimating equations (Proc Genmod) and linear mixed models (Proc Mixed). An alpha level of .05 will be accepted as significant.

Figure 2. Classification of the 17 segments of the left ventricle in bull's-eye view, echocardiographic parasternal short-axis slices, and apical 4- and 2-chamber views.

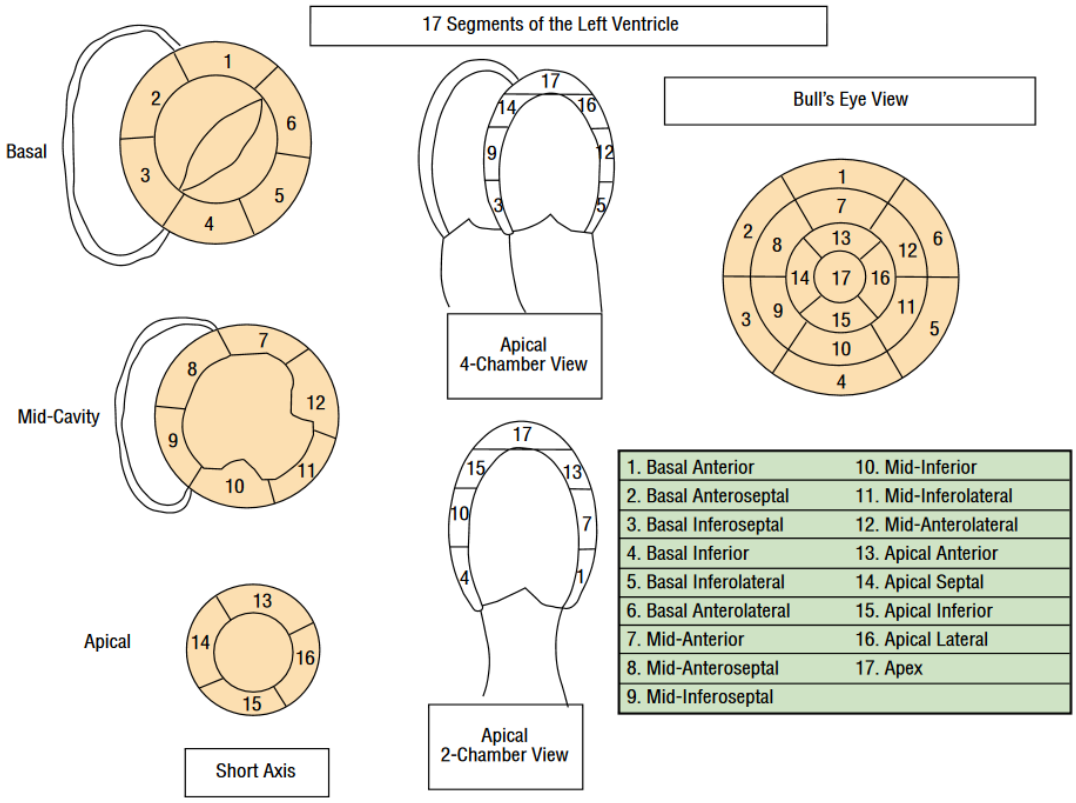
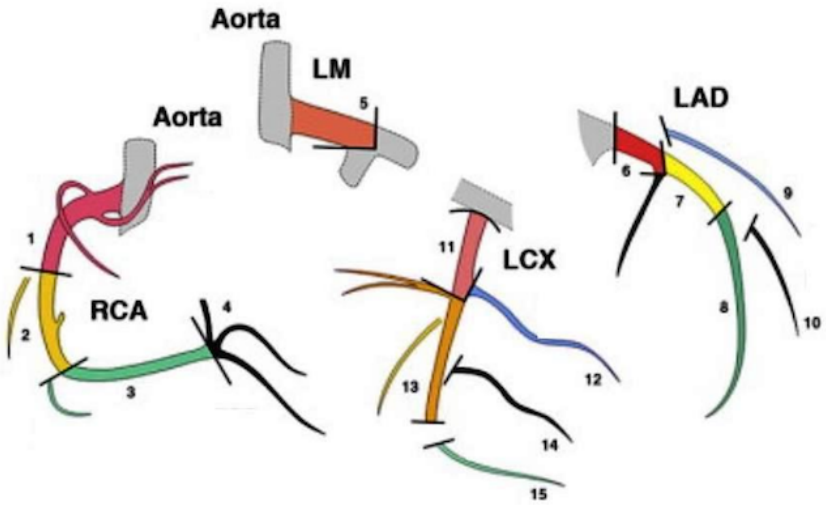


Figure 3. The 15 segments of the coronary arteries. LM: left main coronary; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.



Results

The inclusion of patients in this European cohort began in 2017. Preliminary results are expected to be published in 2019, and complete analysis should be published in 2021.

Discussion

Summary

The MEDIRAD EARLY HEART study is an original multidisciplinary approach to detect and evaluate early radiation-induced cardiotoxicity based on a prospective multicenter cohort study that will finally include 250 patients. It was designed to combine both cardiac imaging information regarding potential early myocardial dysfunction, anatomical coronary changes, and changes in a large panel of circulating cardiac damage biomarkers occurring within first 2 years of RT, based on a precise cardiac dosimetry, allowing to analyze the effect of not only mean heart dose but also doses absorbed by specific heart structures, which better reflect the heterogeneity of dose absorbed by the heart. Provided with patients' own biological, clinical, and dosimetric parameters,

our risk models should allow obtaining individualized risk for patients and enhance knowledge for primary and secondary prevention in these patients.

Strengths and Limitations

A strength of the MEDIRAD EARLY HEART study is the use of ECHO-ST, CTCA, and MRI, which is the most complete approach used for assessing cardiac changes so far. Effects of specific doses to the whole heart and to specific cardiac substructures have only been assessed in a few studies [8,53] that have revealed the importance of better knowledge for assessing the effects of RT to critical structures of the heart, including the effect of both radiation dose and volume of the heart exposed, further illustrated in a previous study that showed that the use of mean heart dose as a surrogate to the coronary doses was not reliable [47,53,54]. This heart substructure dosimetry was retained for the MEDIRAD EARLY HEART study with an automatic method for the treatment of dosimetry that should allow us to obtain consistent results. The approach of simultaneous assessment of multiple biomarkers, including EVs and cardiac miRNAs, has never been used before and should help understand some biological mechanisms involved in the radiation-induced cardiac changes. The study will allow producing short-term results about subclinical cardiac changes but will not produce, at this stage, results on long-term consequences of early cardiovascular changes. The long-term significance of the observed changes will remain an important issue, and our results should help focus on “at-risk” patients for longer follow-ups.

Conclusions

In the context of RT, cardiac risks exist due to the presence of normal cardiac tissue in the irradiated field; this can, unfortunately, affect the quality of life of BC survivors, whose numbers are increasing. As a consequence, there is a need for further research to improve the early detection of late cardiac effects in mostly asymptomatic patients and also to improve the prediction and prevention among these patients [55]. MEDIRAD EARLY HEART results will allow for the optimization of RT protocols, leading to personalized treatments with increased therapeutic efficacy and will, therefore, contribute to improve the radiation protection of BC patients. Additionally, it should improve the prediction and prevention of potential lesions to normal cardiac tissues surrounding tumors and ultimately enhance patients’ care and quality of life.

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Conflicts of Interest

None declared.

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Abbreviations

BC: breast cancer
BLOOD: blood sample for circulating biomarkers
CAC: coronary artery calcium
CAD: coronary artery disease
CT: computed tomography
CTCA: computed tomography coronary angiography
ECHO-ST: two-dimensional speckle-tracking echocardiography
EV: extracellular vesicle
miRNAs: microRNAs
MRI: magnetic resonance imaging
NTCP: Normal Tissue Complication Probability
RT: radiotherapy
UMCG: University Medical Center Groningen

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Protocol

Mobile Phone Text Messaging for Tobacco Risk Communication Among Young Adult Community College Students: Protocol and Baseline Overview for a Randomized Controlled Trial

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Abstract

Background: Community-college students are at high risk for tobacco use. Because the use of mobile phone text messaging is nearly ubiquitous today, short message service (SMS) may be an effective strategy for tobacco risk communication in this population. Little is known, however, concerning the message structure significantly influencing perceived tobacco risk.

Objective: We aim to outline the rationale and design of Project Debunk, a randomized trial comparing the effects of different SMS text message structures.

Methods: We conducted a 6-month randomized trial comparing 8 arms, based on the combination of the 3 message structures delivered to young adults in a 2×2×2 study design: framing (gain-framed or loss-framed), depth (simple or complex), and appeal (emotional or rational). Participants were invited to participate from 3 community colleges in Houston from September 2016 to July 2017. Participants were randomized to 1 arm and received text messages in 2 separate campaigns. Each campaign consisted of 2 text messages per day for 30 days. Perceived tobacco risk was assessed at baseline, 2 months after the first campaign, and 2 months after the second campaign. We assessed the perceived risk of using conventional products (eg, combustible cigarettes) and new and emerging products (eg, electronic cigarettes). The validity of message structures was assessed weekly for each campaign. A 1-week follow-up assessment was also conducted to understand immediate reactions from participants.

Results: We completed data collection for the baseline survey on a rolling basis during this time and assessed the validity of the message structure after 1 week of SMS text messages. For the entire sample (N=636), the average age was 20.92 years (SD 2.52), about two-thirds were male (430/636, 67.6%), and most were black or African American (259/636, 40.7%) or white (236/636, 37.1%). After 1 week of receiving text messages, the following was noted: (a) loss-framed messages were more likely to be perceived as presenting a loss than gain-framed messages ($F_{7,522}$=13.13, P<.001), (b) complex messages were perceived to be more complex than simple messages ($F_{7,520}$=2.04, P=.05), and (c) emotional messages were perceived to be more emotionally involving than rational messages ($F_{7,520}$=6.46, P<.001).

Conclusions: This study confirms that the recruitment, randomization, and message composition have been successfully implemented. Further analyses will identify specific types of messages that are more effective than others in increasing the perceived risk of tobacco use. If our results suggest that any of the 8 specific message structures are more effective for helping young adults understand tobacco risk, this would provide evidence to include such messages as part of a larger technology-based campaign such as mobile phone apps, entertainment-based campaigns, and social media.

Trial Registration: ClinicalTrials.gov NCT03457480; https://clinicaltrials.gov/ct2/show/NCT03457480 (Archived by WebCite at http://www.webcitation.org/6ykd4IIap)

Registered Report Identifier: RR1-10.2196/10977

(JMIR Res Protoc 2018;7(10):e10977) doi:10.2196/10977

KEYWORDS

tobacco use; risk; perception; text messaging; young adult

Introduction

Background

Almost 14% of young adults are currently using cigarettes and 27% have used electronic cigarettes, one of the many new and emerging tobacco products (NETP) [1]. Young adults perceive NETPs such as electronic cigarettes (e-cigarettes) and hookah (ie, waterpipes) as safer ways to enjoy nicotine than conventional products [2-4]. Reduced risk perception has led to uninformed choices among young adults [5], including experimentation with multiple tobacco products, alcohol, and other substances [6-8]. Indicators of socioeconomic disadvantage such as low educational attainment and income status are predictors of tobacco use [9]. In particular, young adults in community college represent an underserved population more susceptible to tobacco use than young adults attending universities or 4-year colleges [10-12].

Following bans on traditional advertising for tobacco, protobacco marketing began to make effective use of modern advertising through social and mobile media channels to reduce the risk perception and promote misinformation about tobacco among young adults [13,14]. Currently, tobacco companies make effective expenditures on product discounts, point-of-sale advertising, direct mail advertising, e-marketing, and social media [15-20]. In addition, with 96% of young adults owning a smartphone, tobacco companies depend on mobile phone strategies for marketing [21]. Tobacco product demonstrations are featured on industry-sponsored websites, and invitations to join Web-based social interactions are encouraged [22-25]. More than 49 protobacco smartphone apps have been identified in app stores under *kids* and *games* categories [26]. As a result, there is a clear need for efforts to respond to protobacco marketing by communicating about tobacco risk to young adults, as delineated by the educational mission and research priorities of the United States Food and Drug Administration [27,28].

The use of mobile health (mHealth) SMS (short message service) text messaging may be an effective strategy for tobacco risk communication to young adults. In the United States, 95% of mobile phones are capable of receiving text messages and 96% of the young adults own mobile phones, indicating this is a highly feasible method for transmitting information to this population [21,29]. Although text messaging programs have been implemented for preventive behavioral interventions, including smoking cessation, no published accounts have applied text messaging to communicate about tobacco risk to young adults [30-34]. To the best of our knowledge, this study is the first to examine different styles of mobile phone text messages for tobacco risk communication. Once the most impactful text messages have been identified, they can subsequently be introduced into an advanced digital intervention that can counteract protobacco marketing.

In the United States, a majority of young adults have smartphones, with more advanced text messaging capabilities (eg, WhatsApp). However, it is pertinent to conduct an evaluation of text messages for risk communication, through traditional text messaging. SMS text messaging ensures that all participants are capable of receiving text messages regardless of a smartphone ownership. In addition, traditional text messaging ensures that all participants receive the messages in the same format, thereby allowing a homogeneous exposure to the intervention content and a more reliable evaluation. Such an evaluation will shed light on how the messages perform. If a set of text messages shows effectiveness, then it can readily be implemented among young adult communities outside the United States, where smartphone capabilities may be limited.

Theoretical Framework

We have designed different types of messages based on 3 main structures: framing (gain-framed or loss-framed messages), depth (ie, simple or complex messages), and appeal (ie, emotional or rational messages) [35-38]. For framing, gain-framed messages describe the benefits of quitting or avoiding tobacco use, whereas loss-framed messages emphasize the disadvantages of use [39-41]. In the context of message depth, both complex grammatical structures and longer words have been applied to shape message complexity [42-45]. In terms of appeal, researchers have developed emotional SMS text messages by introducing emotional words (eg, *happy* and *angry*) [46-48], paralinguistic cues such as vocal spelling (eg, *weeeell* and *soooo*), and emotional icons (eg, ":-)" for a happy face) [49]. Most research has been in gain-framed versus loss-framed text messages [50]. Some literature, predominantly in advertising and promotion, has been dedicated to emotional versus rational appeal [47]. Virtually nothing has been reported on simple versus complex messages in the health risk domain.

The effectiveness of different message characteristics in driving risk communication outcomes stems from the elaboration

likelihood model (ELM) [51,52]. The ELM explains motivation of the individual to engage in information processing. Individuals expending more mental or cognitive effort processing messages tend to formulate stronger attitudes toward an issue and deeper understanding—a desirable attribute for conveying tobacco risk information to the public. One of the basic constructs in the model concerns the degree of cognitive efforts expended and involvement that people use to engage with message content. The ELM posits that individuals can engage in either the central or peripheral processing of health information. Central processing involves attention to message content (eg, complex and rational messages; [53]), whereas peripheral processing involves attention to more peripheral cues such as affect or emotions in developing attitudes toward the message [54]. In the context of risk communication, researchers have not yet presented a theoretical framework supporting certain message types over others with respect to increasing perceived risk. For instance, in the context of message-framing, theoretical frameworks (eg, the prospect theory) do not support a specific framing over another with respect to increasing perceived risk [55]. Instead, such frameworks posit that gain and loss framing can have an effect on health behavior depending on whether the individual is risk-aversive or risk-taking. As a result, theoretical frameworks on message framing have not yet examined perceived risk as the end outcome. In addition, results from previous meta-analyses of relevant research have not been able to favor one message style over another, with respect to health outcomes [56-58]. As a result, it is essential to explore the effect of different message characteristics on perceived risk.

Research Objectives

The primary objective of this study was to conduct exploratory analyses to identify the most effective types of text messages that inform about the harms of tobacco use among young adults in community college. This research protocol outlines the rationale and design of Project Debunk, a community-based randomized trial (peer-reviewed and funded; Multimedia Appendix 1). Project Debunk compares the effects of different structures of text messages delivered to young adults in community college, with the overarching goal of setting the stage for a larger mobile phone text messaging campaign in the future. The protocol presents baseline data from the trial and assesses the validity of the message structures after 1 week of SMS text message exposure.

Methods

Study Design

Project Debunk has gathered data in the following 2 phases: (1) qualitative research for text message development and (2) a randomized trial. This research protocol briefly describes the methods used for the message-development phase and outlines the detailed information about the trial phase at baseline and 1 week after message exposure (ie, the intervention).

In design, the trial is being conducted as a 6-month-long randomized trial comparing 8 arms, based on the combination of the 3 message structures: framing, depth, and appeal (Figure 1). Participants are randomly assigned to one of the 8 arms. They are receiving text messages in 2 separate waves or campaigns. Each campaign consists of 2 text messages per day for 30 days (ie, 60 text messages). The 2 campaigns are 2 months and 1 week apart.

Allowing for a crossover design, participants within each of the 8 arms are randomly divided into 2 groups: group 1 is receiving text messages about conventional tobacco products during campaign 1 and then about NETP during campaign 2. Group 2 is receiving text messages about NETP during campaign 1 and then about conventional tobacco during campaign 2. This crossover design was advised by the Tobacco Center of Regulatory Science on Youth and Young Adults (TX TCORS) Scientific Steering Committee, as it will allow us to explore potential differences between the 2 categories of products within and between participants, with respect to their perceived risk of tobacco use. Data collection for the trial is being conducted at baseline, 2 months post campaign 1 (PC1), 2 months post campaign 2 (PC2), weekly throughout each campaign (a weekly manipulation check assessment), and 7 days after each campaign.

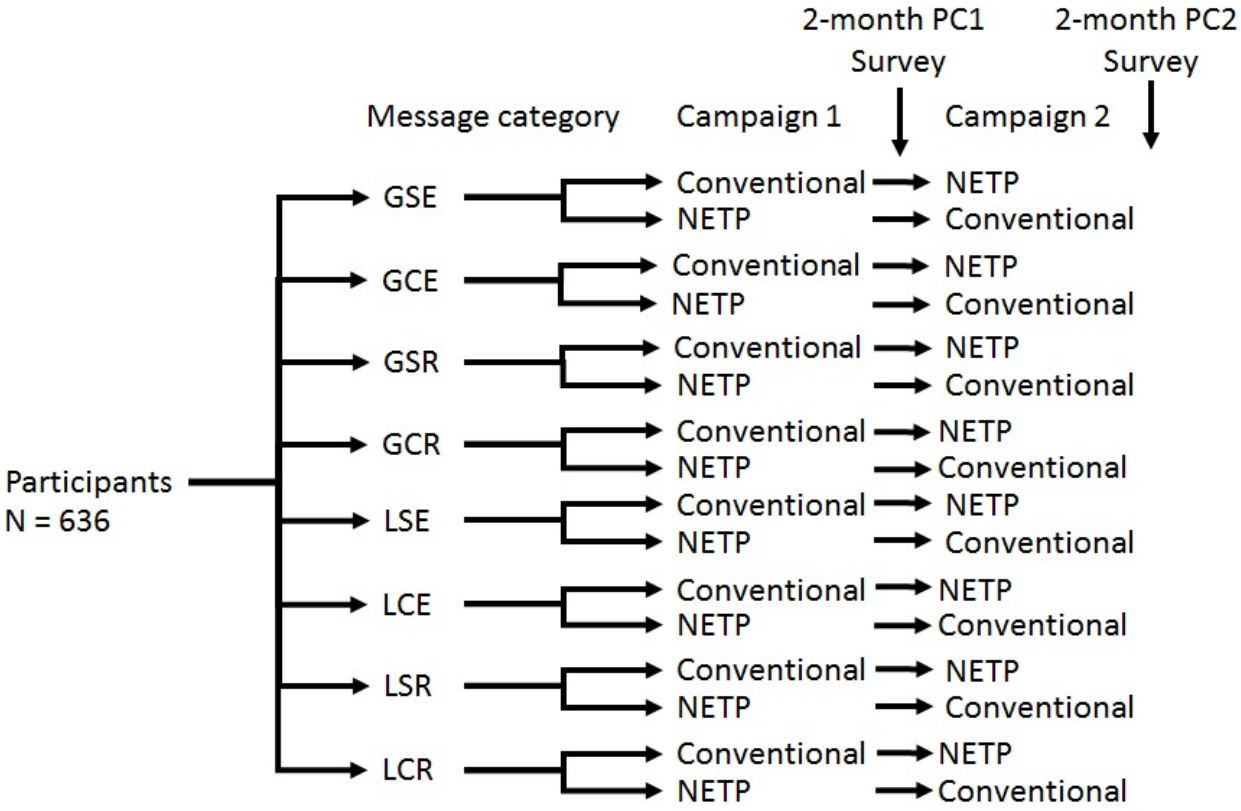
Population

Eligibility criteria for the trial included the following: aged 18 to 25 years, enrolled in community college, using mobile phone text-messaging features on a regular basis, willing to provide their phone number, capable of receiving text messages from our text messaging system, able to read and speak English, and accept to provide a signature on a written informed consent form. The age range of 18 to 25 years was chosen to define emerging young adulthood, as recommended by the National Research Council of the Institute of Medicine in the United States [59]. Three community college campuses from the Houston Community College (HCC) system were targeted for recruitment. Students attending the HCC system are 58% female and have a mean age of 25.6 years. Their racial or ethnic profile is as follows: 30.2% African American, 14.6% Asian American, 14.2% white, 36.9% Hispanic, and 4.2% other [60]. The 3 community colleges were selected based on their ethnically diverse student population and their proximity to our research institution. In addition, we have an existing research relationship with such institutions. All methods and procedures used in the project have been approved by the Institutional Review Board of Ethics of the University of Texas MD Anderson Cancer Center (2014-0474), as well as the HCC System Institutional Review Board.

Recruitment and Enrollment

Recruitment took place at each of the participating HCC campuses from September 2016 to July 2017. We set up recruitment stations or booths equipped with a highly visible logo of the research institution. Printed materials (eg, posters and fliers) announcing the study were displayed in common areas such as student lounges. During participant recruitment at each campus, the research staff explained the purpose of the study to students and answered their questions. Students interested in the trial were screened for eligibility. Subsequently, eligible students provided informed consent to participate in the trial.

Figure 1. Study randomization flowchart. Conventional indicates conventional tobacco products including cigarettes, cigars, smokeless; NETP indicates new and emerging tobacco products, including snus, hookah, and e-cigarettes. In this study design, there is a break of one week between post-campaign 1 survey and campaign 2. GSE: gain-framed, simple emotional; GCE: gain-framed, complex, emotional; GSR: gain-framed, simple, rational; GCR: gain-framed, complex, rational; LSE: loss-framed, simple, emotional; LCE: loss-framed, complex, emotional; LSR, loss-framed, simple, rational; LCR: loss-framed, complex, rational; PC1: post-campaign 1; PC2: post-campaign 2.



Following consent, participants completed a 20-min self-administered baseline survey on their personal mobile phones. This method of enrollment has yielded relatively high recruitment rates (80.1%) during our previous research activities with community college students [61]. Recruitment continued until a sample size of 645 participants was reached. In total, 9 participants were not eligible for the study (over the age of 25 years), so they were dropped, reaching a sample of 636 participants. Up to 6 follow-up reminders were sent via phone and email to remind participants to complete follow-up surveys to progress through the study.

Text Message Interventions for Each Group

From January 2014 to August 2015, our research team from the TX TCORS developed a library of text messages, considering previous scientific literature, developments in social media related to tobacco use, and common terminology. Collectively, the research team has extensive experience in tobacco cessation and prevention, public health, health communication, psychology, and creative writing. Text message design also involved focus group discussions conducted among community college students [62].

Ultimately, our team generated 976 text messages that communicate the risks of tobacco use to college students, both users and nonusers. The messages were developed according to a combination of the 3 structures described above (framing, depth, and appeal), resulting in the following 8 categories:

- Complex, gain-framed, emotional (CGE)
- Complex, gain-framed, rational (CGR)
- Complex, loss-framed, emotional (CLE)
- Complex, loss-framed, rational (CLR)
- Simple, gain-framed, emotional (SGE)
- Simple, gain-framed, rational (SGR)
- Simple, loss-framed, emotional (SLE)
- Simple, loss-framed, rational (SLR)

In addition, for each category, messages were developed to communicate about the harm of conventional tobacco products and NETPs. Messages describing conventional products included information about combustible cigarettes, variants of cigars, cigarillos, and pipes. Messages about NETP included information about e-cigarettes (including other vaping devices), snus, and hookah. Examples of text messages are presented in Multimedia Appendix 2. Experts and students reviewed and rated each message. For validation of message categories, agreement needed to be ≥70% between experts and students for all the 3 message structures. Further validation of message categories was conducted using a linguistic inquiry and word-counting library designed to count words under specific themes (eg, emotional words) [63].

Randomization and Blinding

This is a double-blind study. Following screening and consent, members of our research staff provided participants with a study identification number and a link to the baseline survey to the

mobile phone of each participant. This procedure confirmed that the participant's device fully met the needs of the study. Following the baseline survey, participants were assigned to one of the 8 arms following a computer-generated randomization list using a resource called assessment, intervention, and measurement (AIM). AIM is a centralized repository at the MD Anderson Cancer Center, managed by a team of experts in the science of collecting and managing participant-reported outcomes. The allocation sequence was generated by the AIM system and automatically sent text messages based on allocation, ensuring that our research team is blind to the allocation of each participant. The allocation sequence is password protected and accessible only to nonresearch staff responsible for the AIM system.

Data Collection

Figure 2 depicts how data are collected for the study. Data collection took place at baseline and will continue at the end of each week throughout campaign 1 and campaign 2 of text message dissemination, as well as 7 days PC1, 7 days PC2, 2 months PC1, and 2 months PC2. Participants will provide data through Web-based surveys received through mobile phones.

We developed the surveys with skip patterns to minimize the burden on participants. Using mobile phones from different brands and data carriers, the research team pretested the delivery of surveys and text messages with the assistance of experts in the AIM system (a team of computer scientists and bioinformaticians). This pretesting allowed us to ensure that the surveys and text messages are reachable and readable regardless of the mobile phone or data carrier. We conducted the pretesting initially with our immediate staff and research team. Afterwards, we extended to other staff in one of our departments (Department of Behavioral Science). We conducted an iterative process such that each time an issue was identified by survey testers, it was rectified. Pretesting continued until no issues were reported.

Data collection from the baseline survey ended in July 2017. At the end of each week throughout SMS text message exposure in campaign 1 and campaign 2, participants will complete a manipulation check survey. This weekly manipulation check will ensure that the 8 arms of the study differ with respect to unique features such as perceived emotional level, complexity of the text messages, and framing type. Data collection from the manipulation check survey for the first week of campaign 1 ended in October 2017. Participants will receive a survey regarding their immediate experience with the text messages 7 days PC1 and 7 days PC2. Finally, 2 months PC1 and 2 months PC2, participants will receive a follow-up survey that includes tobacco-related outcome measures.

Survey Measures

All survey measures have been previously tested and validated, with some adaptations (further outlined below). All measures are assessed through Web-based closed surveys. We adhered to the Checklist for Reporting Results of Internet E-Surveys (Multimedia Appendix 3). This checklist will be reported once the study is completed, with the main outcomes of the trial. This paper presents data from the baseline survey and the first weekly manipulation check survey. A detailed description of the main measures and Cronbach alpha values for available data are reported in Multimedia Appendix 4.

Baseline Survey

The baseline survey data for the trial have been collected. With 97 items, baseline information included sociodemographic data such as age, gender, ethnicity, educational attainment, and income [64]. In addition, the baseline survey included questions about factors that may predict perceived risk and tobacco use: mental health status [65], marijuana and alcohol use [64], receptivity to receiving text messages [66], tendency to seek information about tobacco [67], number of friends using tobacco [68], secondhand smoke at home [64], mental health [69], prevention-focus level [70], sensation-seeking level [71], and numeracy ability [72].

Follow-Up Surveys

Follow-up surveys for the trial are ongoing. Weekly manipulation check surveys will assess perceptions of participants about text messages received in the previous week. The perceived message characteristics to be assessed include loss framing [73], message complexity level [74], emotional level of messages [50], credibility [75], message enjoyment [76,77], relevance [78], and message readability.

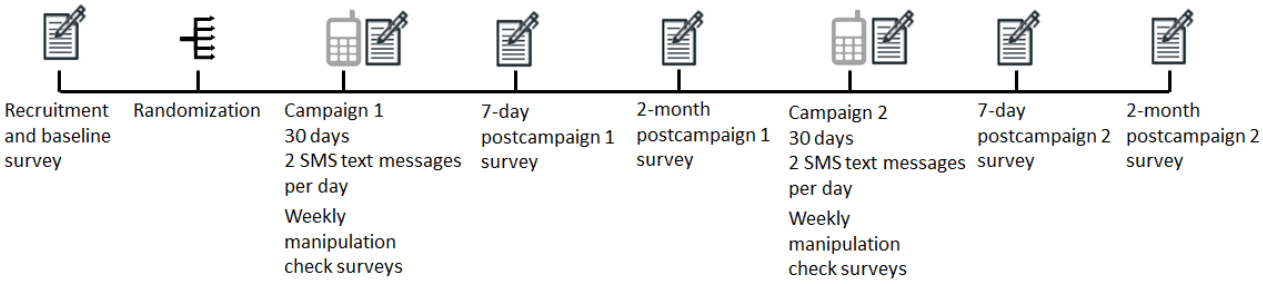
Surveys completed by participants 7 days after each of the 2 campaigns will assess self-reported attention to the text messages [79], emotional involvement [79], thought provocation [80], motivation to discuss the messages with others [81,82], and recall of actual discussions with others about the messages and tobacco [82].

Two months PC1 and 2 months PC2, we will measure perceived risk of using each tobacco product as the main outcome [83]. As secondary outcomes, we will also measure the status and frequency of tobacco use [84], susceptibility to use tobacco products among nonusers (ie, likelihood to initiate use at some point in the future) [85], perceived addictiveness of products [4], perceived popularity of tobacco use [4], and perceived benefits of tobacco use [86].

Compensation

Participants who complete all survey assessments will be compensated a total of US $135. They received a US $25 gift card for completing the baseline survey and will receive a US $25 gift card for completing each of the surveys administered at 2 months after the campaigns. They will also receive a US $10 gift card for completing each of the surveys administered 7 days after the campaigns and a US $5 gift card for each of the 8 weekly manipulation check surveys throughout the 2 campaigns.

Figure 2. Data collection procedure for the study. SMS: short message service.



Attrition and Compliance

To the best of our knowledge, no study examining the effects of different communication styles on risk perception among young adults is currently available. On the basis of the results of a study with community college students by Prokhorov and colleagues [61], we expect an acceptable retention rate (beyond 70%) and high compliance (ie, a self-report of paying attention to and reading most or all of the text messages, with a score of 4 or higher out of 5 on message attention).

Sample Size Determination

For sample size determination, we conducted a power calculation using the outcome of change in perceived risk of cigarette smoking from baseline to 2 months after each of the campaigns. The 8 study arms define a 2×2×2 analysis of variance (ANOVA) factorial design. Assuming a balanced design in each of the 8 study arms for the change in perceived risk, with n=70 per arm, we have at least 80% power to detect an effect size of 0.12 in a fixed-effects ANOVA. A total of 560 participants are needed to provide 70 participants per study arm at 2 months PC2, with complete measurements at baseline. We assume 11% attrition between the assessment at 7 days after the program and 2 months after the program and 1.5% attrition between baseline and the assessment at 2 months PC2 (ie, a total of 12.5% attrition). As a result, our retention rate is expected to be 87.5%. This assumes 640 participants randomized to 8 study arms. This sample size was calculated using PASS 2005 (NCSS, LP).

Current Data Analysis

For the currently available baseline data, we used descriptive statistics to summarize sociodemographic characteristics (eg, age, gender, and race), tobacco-related characteristics (tobacco use and number of friends who use tobacco), and primary psychosocial health outcomes (ie, perceived risk of using each tobacco product).

Using the currently available data from the first weekly manipulation check survey, we checked to make sure that the message structures were perceived by participants as intended. Using one-way ANOVA, we examined study arm differences in perceived message loss framing, complexity level, emotional level, credibility, message enjoyment, perceived message relevance, and perceived message readability. STATA version 14 statistical software was used for data analysis.

Planned Data Analysis

Once the trial is complete, we plan to conduct an exploratory analysis to identify which combination of message characteristics (ie, depth, framing, and appeal) most increases perceived risk of using each type of tobacco product. This analysis is exploratory because to date no theoretical framework or empirical evidence has been presented that demonstrates the importance of one message structure over another in the context of tobacco risk communication. We will first conduct, a series of 8 repeated-measures mixed-effects models for each type of tobacco product with the interaction effect (group [one combination vs all other combinations] × time [baseline, 2 months PC1, and 2 months PC2]) to predict perceived risk of using the product. These models will control for past 30-day use of the product at baseline and the crossover group assignment. In addition to the main outcomes analyses, we plan to conduct several moderation analyses, including the examination of different groups such as gender, race, mental health status, and personality types. This analysis will allow us to check if different types of individuals may respond differently to certain structures of text messages. Repeated-measures mixed-effect models with interaction effects will be conducted. For all data analysis, $P<.05$ is considered statistically significant. We will use STATA version 14 software (StataCorp LLC) for all analyses.

Ethics and Participant Safety

Project Debunk has received full approval from the Research Ethics Board of The University of Texas MD Anderson Cancer Center in Houston, Texas, and it has undergone a local institutional scientific review. To the best of our knowledge, Project Debunk does not pose any significant risks to the physical and psychological safety of participants. Identities of the participants have been coded and only the research team has access to a master list that links names and study codes. This list is kept in a locked file cabinet. Demographic data and assessments of text messages will be stored on secure servers within the institution. Only aggregate data will be reported. We have obtained a Certificate of Confidentiality from the federal government, which will help to protect the privacy of research participants. The certificate protects against the involuntary release of information about participants collected during the course of covered studies.

Results

Status of Results

Data collection is currently underway. Data analysis of change in the main outcomes and writing of the manuscript are expected to be completed in the summer of 2018. We highlight below some of the main baseline findings regarding the study population and measures.

Sociodemographic Characteristics

Table 1 presents sociodemographic characteristics of the respondents. For the entire sample (n=636), the average age was 20.78 years (SD 2.18), about two-thirds (430/636, 67.6%) were male, and most were black or African American (259/636, 40.7%) or white (236/636, 37.1%). With respect to ethnicity, 36.3% (231/636) of participants were Hispanic or Latino. The study arms did not differ in terms of sociodemographic characteristics or mental health status, economic status, planned education level, numeracy ability, prevention-focus level, receptivity to receiving text messages, or sensation-seeking level (Table 1).

Tobacco-Related Characteristics

Tobacco-related characteristics of the respondents are presented in Table 2. Of the entire sample, at least once in their lifetime, 45.1% (287/636) have ever used cigarettes, 32.4% (206/636) have ever used cigars, 55.7% (354/636) have ever used hookah, and 26.9% (171/636) have ever used e-cigarettes. In addition, 25.3% (161/636) have ever used marijuana, 47.2% (300/636) have ever used more than one tobacco product, and 43.2% (275/636) have ever used both marijuana and tobacco products.

Among nonusers, 13.4% (47/351) were found to be susceptible to smoking cigarettes, 24.3% (109/449) were susceptible to smoking cigars, 30.4% (86/283) were susceptible to using hookah, and 24.1% (106/440) were susceptible to using e-cigarettes. At baseline, no significant differences between the 8 groups were found with respect to all such tobacco-related characteristics (Table 2).

Manipulation Checks

We first checked to ensure that the messages were perceived by participants as intended after the first week of message exposure (Table 3). Out of 636 participants, 530 (530/636, 83.3%) completed the manipulation check survey. Compared with gain-framed messages, loss-framed messages were significantly more likely to be perceived as presenting a loss, $F_{7,522}$=13.13, P<.001. Groups receiving CLE, CLR, SLE, and SLR text messages scored higher on perceived message framing as loss than that of groups receiving CGE, CGR, SGE, or SGR text messages. Complex messages were perceived to be significantly more complex than that of simple messages, $F_{7,520}$=2.04, P=.05. Groups receiving CLE, CLR, CGE, and CGR messages scored higher on perceived message complexity than that of groups receiving SLE, SLR, SGE, or SGR messages. Emotional messages were perceived to be significantly more emotionally involving than rational messages, $F_{7,520}$=6.46, P<.001. The groups receiving CLE, SLE, CGE, and SGE messages scored higher on the perceived emotional level of their messages than did the groups receiving CLR, CGR, SLR, or SGR messages (Table 3).

We also checked to make sure that the health messages were consistently perceived as credible (Table 3). As expected, there was no significant difference among the treatment arms with regard to the perceived credibility of message content ($F_{7,520}$=1.70, P=.10). The total mean score on SMS text message credibility was 7.57 (SD 2.01) on an 8-point scale. This confirms that all text message interventions were perceived to be credible sources of information related to tobacco. Similarly, as shown in Table 3, the treatment arms did not differ with regard to the enjoyment of the messages ($F_{7,520}$=0.41, P=.90), perceived message relevance ($F_{7,517}$=1.04, P=.40), or perceived message readability ($F_{7,517}$=0.34, P=.94).

Baseline Treatment Arm Differences in Outcome Measures

At baseline, there were no significant differences among the treatment arms with respect to our risk communication variables: perceived risk of using each tobacco product, perceived personal and general benefits of e-cigarettes, perceived addictiveness of products, or perceived popularity of tobacco use (Table 4).

Table 1. Baseline sociodemographic characteristics for the total sample and by treatment arm.

Characteristics	Statistics[a,b,c]								
	Total	CGE[d]	CGR[e]	CLE[f]	CLR[g]	SGE[h]	SGR[i]	SLE[j]	SLR[k]
Gender at birth (men), n (%)	430 (67.6)	53 (65.4)	52 (67.5)	54 (74.0)	60 (74.1)	56 (65.1)	56 (70.9)	44 (57.1)	55 (67.1)
Race, n (%)									
Hispanic or Latino ethnicity	231 (36.3)	31 (38.3)	29 (37.7)	24 (32.9)	28 (34.6)	30 (34.9)	34 (43.0)	22 (28.6)	33 (40.2)
Asian	99 (15.6)	12 (14.8)	15 (19.5)	13 (17.8)	9 (11.1)	14 (16.3)	7 (8.9)	16 (20.8)	13 (15.9)
Black or African American	259 (40.7)	34 (42.0)	28 (36.4)	33 (45.2)	39 (48.1)	33 (38.4)	30 (38.0)	31 (40.3)	31 (37.8)
White	236 (37.1)	31 (38.3)	29 (37.7)	21 (28.8)	29 (35.8)	36 (41.9)	31 (39.2)	24 (31.2)	35 (42.7)
Other	42 (6.6)	4 (4.9)	5 (6.5)	6 (8.2)	4 (4.9)	3 (3.5)	11 (13.9)	6 (7.8)	3 (3.7)
Have children, n (%)	58 (9.1)	7 (8.6)	8 (10.4)	8 (11.0)	5 (6.2)	5 (5.8)	9 (11.4)	9 (11.7)	7 (8.5)
Age (years), mean (SD)	20.92 (2.52)	20.53 (2.21)	21.03 (2.10)	20.75 (2.10)	20.89 (2.30)	20.55 (2.06)	20.97 (2.25)	20.86 (2.22)	20.66 (2.22)
Mental health status, mean (SD)	67.33 (19.18)	67.80 (18.01)	64.83 (18.80)	68.11 (19.16)	69.43 (19.32)	67.53 (18.74)	68.30 (19.02)	67.17 (20.42)	65.46 (20.33)
Economic status, mean (SD)	2.77 (0.92)	2.67 (0.96)	2.79 (0.96)	2.74 (0.96)	2.68 (0.93)	2.84 (0.89)	2.96 (0.81)	2.77 (0.97)	2.71 (0.90)
Planned education level, mean (SD)	3.67 (1.15)	3.77 (1.10)	3.75 (1.05)	3.53 (1.28)	3.81 (1.16)	3.66 (1.06)	3.72 (1.09)	3.52 (1.25)	3.61 (1.24)
Numeracy ability, mean (SD)	5.35 (1.81)	5.41 (1.61)	5.51 (1.82)	5.29 (2.00)	5.15 (2.04)	5.56 (1.69)	5.20 (1.86)	5.39 (1.73)	5.27 (1.74)
Prevention-focus level, mean (SD)	2.81 (0.69)	2.73 (0.71)	2.90 (0.73)	2.86 (0.67)	2.77 (0.72)	2.80 (0.70)	2.80 (0.64)	2.79 (0.72)	2.82 (0.68)
Receptivity to receiving text messages, mean (SD)	0.92 (0.15)	0.94 (0.12)	0.90 (0.22)	0.90 (0.15)	0.89 (0.18)	0.92 (0.13)	0.95 (0.11)	0.94 (0.10)	0.93 (0.14)
Sensation-seeking level, mean (SD)	3.50 (0.83)	3.50 (0.73)	3.47 (0.85)	3.34 (0.91)	3.45 (0.86)	3.56 (0.78)	3.60 (0.84)	3.51 (0.85)	3.55 (0.81)

[a]Missing values are not presented in this table.

[b]Participants were randomized to one of the 8 treatment arms, describing the type of messages.

[c]Proportions in subsample and percentage are presented for categorical variables, and the mean with SD are presented for continuous variables.

[d]CGE: complex, gain-framed, emotional.

[e]CGR: complex, gain-framed, rational.

[f]CLE: complex, loss-framed, emotional.

[g]CLR: complex, loss-framed, rational.

[h]SGE: simple, gain-framed, emotional.

[i]SGR: simple, gain-framed, rational.

[j]SLE: simple, loss-framed, emotional.

[k]SLR: simple, loss-framed, rational.

Table 2. Tobacco-related characteristics for the total sample and by the group at baseline.

Substance use[a]	N[b] (%)								
	Total	CGE[c]	CGR[d]	CLE[e]	CLR[f]	SGE[g]	SGR[h]	SLE[i]	SLR[j]
Cigarettes									
Ever	287 (45.1)	37 (45.7)	34 (44.2)	28 (38.4)	35 (43.2)	43 (50.0)	41 (51.9)	35 (45.5)	34 (41.5)
p30[k]	87 (13.7)	12 (14.8)	7 (9.1)	9 (12.3)	14 (17.3)	11 (12.8)	11 (13.9)	12 (15.6)	11 (13.4)
Cigars									
Ever	206 (32.4)	27 (33.3)	29 (37.7)	29 (39.7)	22 (27.2)	20 (23.3)	28 (35.4)	25 (32.5)	26 (31.7)
p30	61 (9.6)	2 (7.4)	11 (14.3)	4 (5.5)	9 (11.1)	8 (9.3)	10 (12.7)	4 (5.2)	9 (11.0)
Smokeless									
Ever	33 (5.2)	2 (2.5)	1 (1.3)	6 (8.2)	3 (3.7)	2 (2.3)	9 (11.4)	6 (7.8)	4 (4.9)
p30	5 (0.8)	1 (1.2)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)
Hookah									
Ever	354 (55.7)	42 (51.9)	43 (55.8)	34 (46.6)	46 (56.8)	52 (60.5)	46 (58.2)	44 (57.1)	47 (57.3)
p30	116 (18.2)	16 (19.8)	15 (19.5)	8 (11.0)	15 (18.5)	18 (20.9)	15 (19.0)	15 (19.5)	14 (17.1)
e-Cigarettes									
Ever	171 (26.9)	22 (27.2)	19 (24.7)	19 (26.0)	21 (25.9)	26 (30.2)	22 (27.9)	20 (26.0)	22 (26.8)
p30	50 (7.9)	5 (6.2)	5 (6.5)	7 (9.6)	7 (8.6)	13 (15.1)	5 (6.3)	6 (7.8)	2 (2.4)
Marijuana	161 (25.3)	21 (25.9)	24 (31.2)	15 (20.6)	21 (25.9)	22 (25.6)	24 (30.4)	17 (22.1)	17 (20.7)
Poly-tobacco use[k]	300 (47.2)	43 (53.1)	34 (44.2)	35 (48.0)	39 (48.2)	40 (46.5)	42 (53.2)	34 (44.2)	33 (40.2)
Susceptibility to use[l]									
Cigarettes	46 (13.2)	7 (15.9)	2 (4.7)	2 (4.4)	9 (19.6)	7 (18.3)	6 (15.8)	4 (9.5)	9 (18.8)
Cigars	96 (22.7)	14 (24.1)	4 (7.8)	7 (14.9)	19 (29.2)	18 (26.1)	10 (16.7)	10 (18.2)	14 (23.7)
Smokeless	80 (13.3)	14 (17.7)	5 (6.6)	7 (10.5)	13 (16.7)	10 (11.9)	8 (11.4)	10 (14.1)	13 (16.7)
Hookah	85 (30.1)	19 (48.7)	6 (17.7)	12 (30.8)	10 (28.6)	11 (32.4)	8 (24.2)	6 (18.2)	13 (37.1)
e-Cigarettes	125 (26.9)	21 (35.59)	13 (22.4)	11 (20.4)	16 (26.7)	13 (21.7)	18 (31.6)	14 (24.6)	19 (31.7)
Use marijuana and tobacco	275 (43.2)	40 (49.4)	39 (50.6)	26 (35.6)	34 (42)	38 (43.7)	32 (40.5)	31 (40.3)	35 (42.7)
Secondhand smoke in house	68 (10.7)	10 (12.3)	9 (11.7)	10 (13.7)	7 (8.6)	6 (6.9)	4 (5.1)	12 (15.6)	10 (12.2)
Have friends who use tobacco	566 (89.0)	76 (93.8)	67 (87.0)	60 (82.2)	68 (84.0)	80 (92.0)	69 (87.3)	72 (93.5)	74 (90.2)

[a]Results that include *Ever* product use followed by *Past 30 days* use (p30).

[b]Randomization of participants to 8 groups of short message service text messages.

[c]CGE: complex, gain-framed, emotional.

[d]CGR: complex, gain-framed, rational.

[e]CLE: complex, loss-framed, emotional.

[f]CLR: complex, loss-framed, rational.

[g]SGE: simple, gain-framed, emotional.

[h]SGR: simple, gain-framed, rational.

[i]SLE: simple, loss-framed, emotional.

[j]SLR: simple, loss-framed, rational.

[k]Refers to the concurrent use of multiple tobacco products among participants at any time.

[l]Susceptibility to use is measured with nonusers only.

Table 3. Week 1 manipulation check outcomes for the total sample and by treatment arm.

Outcomes[a,b]	Mean (SD)									*P* value[k]
	Total	CGE[c]	CGR[d]	CLE[e]	CLR[f]	SGE[g]	SGR[h]	SLE[i]	SLR[j]	
Perceived message-framing as a loss (8-point scale)	5.20 (3.22)	3.74 (2.23)	4.39 (3.00)	5.74 (3.25)	7.58 (2.86)	4.07 (2.66)	4.17 (3.04)	6.06 (3.33)	6.00 (3.41)	<.001
Perceived complexity level (8-point scale)	2.98 (2.02)	3.07 (2.12)	2.81 (2.26)	3.34 (2.33)	3.60 (2.14)	2.45 (1.54)	2.86 (1.95)	3.05 (1.96)	2.78 (1.81)	.05
Perceived emotional level (8-point scale)	3.35 (2.23)	3.72 (2.13)	2.24 (1.52)	4.39 (2.72)	3.39 (2.33)	3.62 (2.22)	2.80 (1.90)	3.82 (2.28)	2.86 (1.97)	<.001
Perceived credibility (8-point scale)	7.57 (2.01)	7.43 (1.85)	8.01 (1.78)	7.60 (1.90)	7.87 (1.80)	6.98 (2.45)	7.70 (1.96)	7.36 (2.01)	7.64 (2.09)	.10
Enjoyment of messages (8-point scale)	5.90 (1.49)	5.87 (1.46)	5.78 (1.37)	6.13 (1.57)	5.93 (1.46)	5.93 (1.54)	5.78 (1.47)	5.96 (1.56)	5.80 (1.53)	.90
Perceived relevance (5-point scale)	2.37 (0.85)	2.37 (0.87)	2.40 (0.91)	2.38 (0.81)	2.57 (0.79)	2.22 (0.81)	2.41 (0.83)	2.26 (0.94)	2.40 (0.81)	.40
Perceived readability (5-point scale)	3.46 (0.78)	3.41 (0.81)	3.44 (0.84)	3.51 (0.75)	3.45 (0.85)	3.53 (0.70)	3.50 (0.75)	3.36 (0.84)	3.49 (0.71)	.93

[a]Missing values are not presented in this table. Out of 636 participants, 530 (530/636, 83.3%) completed the manipulation check survey.

[b]Participants were randomized to one of the 8 treatment arms, describing the type of messages.

[c]CGE: complex, gain-framed, emotional.

[d]CGR: complex, gain-framed, rational.

[e]CLE: complex, loss-framed, emotional.

[f]CLR: complex, loss-framed, rational.

[g]SGE: simple, gain-framed, emotional.

[h]SGR: simple, gain-framed, rational.

[i]SLE: simple, loss-framed, emotional.

[j]SLR: simple, loss-framed, rational.

[k]Significance testing with analysis of variance.

Table 4. Baseline risk communication outcomes for the entire sample and by treatment arm.

Outcome[a]	Mean (SD)								
	Total	CGE[b]	CGR[c]	CLE[d]	CLR[e]	SGE[f]	SGR[g]	SLE[h]	SLR[i]
Perceived risk of using cigarettes	3.69 (0.55)	3.76 (0.49)	3.68 (0.52)	3.78 (0.35)	3.68 (0.6)	3.57 (0.65)	3.70 (0.56)	3.75 (0.47)	3.60 (0.63)
Perceived risk of using cigars	3.61 (0.56)	3.67 (0.49)	3.64 (0.5)	3.63 (0.52)	3.62 (0.56)	3.51 (0.62)	3.65 (0.56)	3.62 (0.54)	3.52 (0.67)
Perceived risk of using smokeless tobacco	3.48 (0.60)	3.49 (0.57)	3.44 (0.60)	3.59 (0.49)	3.47 (0.68)	3.45 (0.61)	3.48 (0.60)	3.56 (0.53)	3.38 (0.68)
Perceived risk of using hookah	3.09 (0.8)	3.00 (0.87)	3.15 (0.71)	3.37 (0.72)	3.09 (0.79)	2.99 (0.84)	3.13 (0.79)	3.11 (0.77)	3.01 (0.85)
Perceived risk of using e-cigarettes	3.06 (0.83)	2.98 (0.82)	3.17 (0.65)	3.31 (0.77)	3.08 (0.8)	2.98 (0.9)	3.11 (0.84)	3.04 (0.84)	2.96 (0.94)
Perceived personal benefits of e-cigarettes	0.88 (0.76)	0.87 (0.77)	0.88 (0.73)	1.02 (0.87)	0.76 (0.65)	0.91 (0.8)	0.85 (0.77)	0.89 (0.72)	0.85 (0.74)
Perceived general benefits of e-cigarettes	1.41 (0.69)	1.47 (0.51)	1.53 (0.68)	1.42 (0.69)	1.39 (0.72)	1.45 (0.78)	1.31 (0.77)	1.37 (0.73)	1.38 (0.64)
Perceived addictiveness of products	1.23 (0.59)	1.23 (0.53)	1.26 (0.56)	1.33 (0.59)	1.21 (0.64)	1.24 (0.55)	1.18 (0.62)	1.23 (0.61)	1.18 (0.61)
Perceived popularity of tobacco use	2.44 (1.13)	2.57 (1.11)	2.5 (1.05)	2.33 (1.21)	2.36 (1.15)	2.47 (1.09)	2.49 (1.06)	2.28 (1.19)	2.48 (1.2)

[a]Participants were randomized to one of the 8 treatment arms, describing the type of messages.

[b]CGE: complex, gain-framed, emotional.

[c]CGR: complex, gain-framed, rational.

[d]CLE: complex, loss-framed, emotional.

[e]CLR: complex, loss-framed, rational.

[f]SGE: simple, gain-framed, emotional.

[g]SGR: simple, gain-framed, rational.

[h]SLE: simple, loss-framed, emotional.

[i]SLR: simple, loss-framed, rational.

Discussion

Overview

The Project Debunk trial will evaluate a comprehensive campaign delivered by mobile phone for increasing tobacco risk perception among a large sample of young adults in community college, including both tobacco users and nonusers. In particular, the trial will identify which structures of SMS text messages, if any, have the strongest effect on increasing the perceived risk of using conventional tobacco products and NETP. The results of this study will form the basis of an evidence-based resource that future researchers and practitioners could modify for use among their populations of interest.

To the best of our knowledge, this is the first published mHealth protocol for a trial that assesses the effect of a comprehensive and evidence-based mobile phone text messaging campaign for tobacco risk communication. This protocol summarizes the design and describes the planned evaluation of Project Debunk. Going beyond a simple presentation of our future study procedures, the protocol also presents the results from our baseline data. In particular, baseline information confirms that a substantial proportion of young adults at community colleges continue to smoke cigarettes, in addition to using NETP such as e-cigarettes and hookah. There were no differences among the treatment arms with respect to sociodemographic or tobacco-related characteristics. In addition, the treatment arms did not differ at the baseline with respect to the perceived risk of using any tobacco product. Preliminary results also show that we have successfully manipulated the 8-message structure combinations with our study sample. This is evident from treatment arm differences with respect to perceived message loss framing, emotional level, and complexity. All 8-message structure combinations were found to be enjoyable, easy to read, and credible.

Anticipated Results

On the basis of previous pilot data collected by our team [62], we anticipate adequate feasibility and satisfaction among participants. In a previous study that we conducted with young adult college students [61], the recruitment rate was high (80.1%) and participants reported positive changes in their perceived risk of tobacco use. We anticipate similar results in Project Debunk for all groups. We project that all message structure combinations will result in an increase in perceived risk of using tobacco products. As suggested by recent reports [4,87], we expect higher levels of perceived risk of using combustible cigarettes compared with NETP such as e-cigarettes

and hookah. In addition, change over time in perceived risk is expected to be lower for combustible cigarettes, compared with e-cigarettes and hookah. We cannot predict or anticipate specific results with respect to which message structure is most effective in improving tobacco risk perception. This study will be the first to provide empirical evidence that highlights the importance of one message structure over another in the context of tobacco risk communication. Once the successful types of text messages have been identified, our future plan is to introduce the messages in the context of an advanced digital intervention that can effectively communicate tobacco risk.

Strengths and Limitations

We will address the anticipated difficulties described in previous studies of mobile phone text messaging in young-adult populations [88-90], such as participant retention, in several ways: regular communication with participants and continuous reminders via phone, and compensation (gift cards) at project completion. This study has a convenience sample. Nevertheless, our sample is representative of the community college population in age, gender, and ethnicity. It also involves a heterogeneous ethnic distribution, with a proportion of tobacco users and demographics that are similar to that of young adults in the state of Texas [91].

Conclusions

It is evident that young adult tobacco users and nonusers are interested in mHealth programs that help them learn about tobacco risks [62]. Moreover, as a mass media strategy, mHealth programs offer the potential to greatly increase the reach of young adults. If our results suggest that a specific mobile phone text message structure is most effective for helping young adults accurately perceive tobacco risk, this would provide evidence to include such text messages as part of larger technology-based campaigns such as smartphone apps, entertainment-based campaigns, and social media. These findings would also provide a deeper understanding of the factors that drive change in the perceived risk of using tobacco and improve the design of our text messages. Considering the wide variety of tobacco products studied in the trial, the results will highlight any potential differences between the products. With the use of mHealth text messaging, the results of this study will reveal the best strategies to efficiently and widely communicate risk to young adults and ultimately prevent tobacco use in this age demographic.

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Authors' Contributions

AVP and KSC conceptualized the initial study with numerous valuable contributions by GEK. TCM, SR, KWC, and GCB managed recruitment and will manage follow-up assessments. GEK wrote the preliminary manuscript. GEK and MC conducted the statistical analysis. AVP, CLP, DJV, KSC, TCM, and AP contributed to drafts of the manuscript. AVP approved the final manuscript. Authors GEK and MC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report from the Food and Drug Administration of the National Institutes of Health.

[PDF File (Adobe PDF File), 146KB - resprot_v7i10e10977_app1.pdf]

Multimedia Appendix 2

Examples of text messages.

[PDF File (Adobe PDF File), 104KB - resprot_v7i10e10977_app2.pdf]

Multimedia Appendix 3

Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

[PDF File (Adobe PDF File), 118KB - resprot_v7i10e10977_app3.pdf]

Multimedia Appendix 4

Description of the main measures.

[PDF File (Adobe PDF File), 51KB - resprot_v7i10e10977_app4.pdf]

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Abbreviations

AIM: assessment, intervention, and measurement
ANOVA: analysis of variance
CGE: complex, gain-framed, emotional
CGR: complex, gain-framed, rational
CLE: complex, loss-framed, emotional
CLR: complex, loss-framed, rational
e-cigarettes: electronic cigarettes
ELM: elaboration likelihood model
HCC: Houston Community College
mHealth: mobile health
NETP: new and emerging tobacco products
PC1: postcampaign 1
PC2: postcampaign 2
SGE: simple, gain-framed, emotional
SGR: simple, gain-framed, rational
SLE: simple, loss-framed, emotional
SLR: simple, loss-framed, rational
SMS: short message service
TX TCORS: Tobacco Center of Regulatory Science on Youth and Young Adults

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Protocol

Hispanic Secondary Stroke Prevention Initiative Design: Study Protocol and Rationale for a Randomized Controlled Trial

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Abstract

Background: Hispanic-Latino populations face a disproportionate stroke burden and are less likely to have sufficient control over stroke risk factors in comparison with other ethnic populations. A promising approach to improving chronic health outcomes has been the use of community health workers (CHWs).

Objective: The objective of this randomized controlled trial is to evaluate the effectiveness of a CHW intervention among Latino patients at risk of recurrent stroke.

Methods: The Hispanic Secondary Stroke Prevention Initiative (HiSSPI) is a randomized clinical trial of 300 Latino participants from South Florida who have experienced a stroke within the last 5 years. Participants randomized into the CHW intervention arm receive health education and assistance with health care navigation and social services through home visits and phone calls. The intervention also includes a mHealth component in which participants also receive daily text messages (short message service). The primary outcome is change in systolic blood pressure at 12 months. Other secondary outcomes include changes in low-density lipoprotein, glycated hemoglobin, and medication adherence.

Results: Study enrollment began in 2015 and will be completed by the end of 2018. The first results are expected to be submitted for publication in 2020.

Conclusions: HiSSPI is one of the first randomized controlled trials to examine CHW-facilitated stroke prevention and will provide rigorous evidence on the impact of CHWs on secondary stroke risk factors among Latino individuals who have had a stroke.

Trial Registration: ClinicalTrials.gov NCT02251834; https://clinicaltrials.gov/ct2/show/NCT02251834 (Archived by WebCite at http://www.webcitation.org/72DgMqftq)

International Registered Report Identifier (IRRID): RR1-10.2196/11083

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KEYWORDS

Hispanics; Latinos; stroke; community health care; community health workers; randomized controlled trial; health care disparities; mobile phones; mHealth

Introduction

Background

With 795,000 annual cases, stroke is a leading cause of death and the single greatest cause of preventable adult disability in the United States [1]. Medical costs, medication, and lost productivity resulting from stroke cost an estimated US $34 billion annually [1]. Moreover, as our population ages, the stroke incidence is expected to increase dramatically. By 2035, an additional 3.7 million people are expected to have suffered from a stroke, resulting in a two-fold increase in health care costs [2].

Nearly 23% of stroke cases are recurrent strokes [1], and the risk of recurrence ranges from 14% to 40% within a 5-year period following the first attack [3]. Further, the adverse impact of recurrent stroke is more devastating than the initial attack; the fatality rate during the first 30 days after a recurrent stroke is more than double the fatality rate among first-time stroke victims [4]. Research indicates that the majority of recurrent stroke cases can be prevented by better control of modifiable risk factors [5]. However, Hispanic individuals (a term we used interchangeably with Latinos) face a disparate burden of stroke and stroke risk factors compared with non-Hispanic white individuals [6,7,8]; for example, hypertension, diabetes, and limited physical activity account for more strokes among Hispanic individuals than any other racial or ethnic group [9,10,11].

Hispanic individuals are also less likely to receive evaluation or treatment for hypertension or diabetes and are also less likely to maintain their treatment regimens after diagnosis [10,12]. Socioeconomic barriers such as lack of insurance, limited language, competing demands, and inadequate care access also disproportionately impact the Hispanic population, which further compound their health risks [13,14].

Prior Work

A promising approach to improving disease outcomes among Hispanic individuals has been the use of community health workers (CHWs) [15]. CHWs are trusted members of a target community who understand the local health beliefs and recognize the social and historical experiences shaping their communities [15,16]. They serve as links between their communities and the health care system, acting as patient advocates, delivering prevention education and counseling services, and linking people to the appropriate care facilities [17]. There has been increasing evidence on CHWs for a variety of preventive and chronic conditions [16], including knowledge and behaviors aimed at vascular risk factors and self-management [18-20]. Although more limited, randomized studies have also shown that CHW interventions can improve physiological outcomes such as glycemic control [21].

Another approach of increasing interest in addressing disparities has been the use of mHealth devices and technologies. These approaches allow clinicians and researchers to provide health services through platforms such as short message service (SMS) text messaging, Web-based services, and dedicated phone apps [22]. With over 80% of minority adults having a cellular phone for phone calls or SMS text messaging [23], mHealth technologies are a potentially cost-effective way of delivering some health services to underserved populations [24,25].

Combined CHW interventions and mHealth approaches may be a potentially innovative approach to address the care of Hispanic stroke patients. Although there are increasing reports of mHealth-focused CHW project evaluations, the majority of studies are not randomized and provide limited information on the impact of the intervention [26]. One recent large randomized study among low-income patients with uncontrolled hypertension in Argentina reported that a CHW intervention that included SMS text messaging improved the proportion of patients, with controlled blood pressure increasing from 17.0% at baseline to 72.9% at 18 months in the intervention group and from 17.6% to 52.2% in the usual care group [27].

Study Goals

To examine the impact of such an approach in the prevention of secondary stroke among Latinos, we designed a clinical trial consisting of a combined CHW and mHealth intervention. We examine the effectiveness of such a combined intervention in lowering of systolic blood pressure, which is the most important modifiable risk factor for recurrent stroke.

Methods

Overview and Conceptual Design

The Hispanic Secondary Stroke Prevention Initiative (HiSSPI) is a randomized single-blind, parallel-controlled trial of 300 Latino patients who have experienced an ischemic or hemorrhagic stroke in the last 5 years. The theoretical foundation of the HiSSPI study is grounded in the Chronic Care Model, an organizational framework for restructuring chronic disease management to create a partnership between health systems and communities [28]. The focus of our design emphasizes a community-based approach to successfully linking individuals in underserved populations with effective health care services [15,16]. The study was reviewed and approved by the University of Miami Institutional Review Board and is registered with ClinicalTrials.gov (NCT02251834).

Study Setting

The study took place in Miami-Dade County, where Latinos compromise 68% of the population [29,30]. Unlike other parts of the country, the Latino population of the county is highly diverse, having ethnic origins from most countries in Latin America. As an example, Miami-Dade has the highest number of Cubans, Colombians, Hondurans, and Peruvians in the United States [31].

For this study, patients were recruited from the following 2 health systems in Miami's Civic Center Health District: the University of Miami Health System (UHealth) and Jackson Health System. UHealth is a private, University-owned not-for-profit health care system, and Jackson Health System is a public safety-net hospital system. Both are quaternary care institutions and major teaching sites for the University of Miami Miller School of Medicine. Additionally, both systems are

Florida-designated Primary Stroke Centers and see over 1000 stroke admissions per year combined.

Study Participants: Inclusion and Exclusion Criteria

Eligible patients are Miami-Dade residents aged 18 or older, who self-identify as Hispanic or Latino, and who were admitted to the stroke service for an intracerebral hemorrhage or ischemic hemorrhagic stroke. Initially, the study was designed to recruit patients having had a stroke admission within the last month, but a year after the study began, inclusion criteria were expanded to any patient having had a documented admission for stroke within the last 5 years.

Because the study is aimed at preventing a secondary stroke, the focus was on stroke patients whose initial stroke was not very severe. Stroke severity is assessed using the modified Rankin Scale [32,33]. This scale evaluates a stroke patient's degree of disability that resulted from the stroke. Patients can score on a range from 0 (no residual symptoms) to 6 (death). For study eligibility, patients must have an modified Rankin Scale score no greater than 3, which means they may have up to a moderate disability from the stroke but can still walk without assistance. Patients who have any immediate or life-threatening morbidity (eg, active cancer), those with an arm circumference greater than 47 cm (automated cuffs are unreliable at greater arm widths), or who are currently enrolled in another stroke, cardiovascular, or diabetes study were excluded from the study.

Recruitment: Participant Selection

Recruitment began in February 2015 and will be carried out over the 5-year study period. Study recruitment uses a multimodal approach. One approach is having study coordinators track and review data on all stroke admissions at both Jackson Health System and UHealth. Study coordinators approach patients, describe the study in person while patients are in the hospital, provide interested participants with brochures detailing the study program, and collect detailed contact information. When not possible in person, this is done via phone after discharge.

As noted above, a year after the study began recruitment, inclusion criteria were expanded to any patient having had a documented admission for stroke within the last 5 years. This allowed coordinators to recruit from the stroke clinic through provider referrals. It also allowed for recruitment from an existing stroke registry. Patients enrolled in others stroke projects were also referred to us after they completed participation in their other studies.

Consent and Enrollment

Identified participants are contacted via phone to assess their interest in participation, evaluate their study eligibility, and answer any questions. If the patient is interested and qualifies for participation, they are scheduled for a baseline appointment at the Clinical Research Center at the University of Miami. At the appointment, the study is again explained, and informed consent is obtained. Vital signs are measured and blood was collected, and a baseline questionnaire is subsequently administered. The project coordinator orally administers the survey and records participant responses into an electronic data management system (Research Electronic Data Capture) via laptop computer [34]. To ensure accuracy, baseline sessions are also audiorecorded and periodically reviewed for concordance with the data electronically entered.

The full baseline process takes approximately 90 minutes to complete. Participants receive US $50 compensation to cover the cost of travel and other incidentals once they have completed the full assessment. Upon completing the baseline, participants are randomized into 1 of 2 research arms by the project biostatistician.

Randomization and Blinding

Patients are randomized at a 1:1 ratio to the enhanced care group or the CHW intervention group within each hospital. Within each site, every eligible patient receives a unique study subject identification number and the prespecified assignment that corresponds to the identification number through randomization. The principal investigator and the program clinical coordinator are blinded to study allocation. However, both participants and CHWs are aware of the group to which each participant was randomized.

Control Arm: Enhanced Usual Care

Patients randomized into this group receive enhanced usual care. Depending on the stroke severity, patients at both facilities are either discharged home or to a short-term rehabilitation facility. Prior to release, the patient's nurse or case manager ensures the patient is scheduled for a follow-up with their primary care provider and a neurologist. Patients lacking a primary care provider are provided with a list of potential follow-up care facilities and information on how to schedule an appointment.

For this project, participants in the control group also receive health education materials every 4 months including the following: "Lo que necesita saber sobre los ataques cerebrales," a National Institute of Neurological Disorders and Stroke brochure that explains the causes of stroke, the associated risk factors, and strategies for prevention [35]; "Cómo prepararse para una cita con el medico," a booklet that provides guidance, strategies, and tips to Latino patients on ways to better communicate with their physician [36]; and a National Heart, Lung, and Blood Institute bilingual Latino recipe cookbook [37].

Community Health Worker Intervention

Through home visits and phone contact, CHWs empower patients with skills to manage their health including medication adherence, physical activity, nutrition, and mental well-being.

Hiring and Training of Community Health Workers

The lead CHW for HiSSPI (OF) is a bilingual Florida-certified CHW [38] with several years of CHW experience. She has worked with our team on a previous diabetes intervention study [20]. In selecting additional CHWs to work on HiSSPI, we prioritize bilingual candidates with knowledge of the local community and prior experience in service delivery (eg, social, medical, education, consumer) to Latino populations. Other important selection criteria include maturity, communication

skills, and prior positive work evaluations. CHWs also need to meet the basic requirements to be a Florida-certified CHW. A personal vehicle and valid driver's license are also required.

For HiSSPI training, CHWs need to complete "Promoting Healthy Choices and Community Changes," a 3-hour Web-based training provided by the Department of Health and Human Services Promotores de Salud Health Initiative [39]. This 4-part learning program gives CHWs health training on reaching vulnerable, low-income, and underserved members of Latino and Hispanic populations. For the cardiovascular disease-specific training, we use CHW training materials from the Centers for Disease Control and Prevention and National Heart, Lung, and Blood Institute as well as our own CHW training material [40-42]. Additional training on stroke and stroke prevention is also provided by the stroke neurologist on our team (JGR).

CHWs also receive ongoing training including continuing education modules on topics such as motivational interviewing, clinic and insurance navigation, cardiovascular disease care, and social support resource navigation. Additionally, weekly meetings are held with a CHW supervisor to obtain performance feedback and discuss individual cases. CHWs are further required to complete all University of Miami and National Institutes of Health required training in human subject research and HIPPA as well as specific research training that we developed for CHWs [43]. Textbox 1 provides additional details on these training modules.

Intervention Enhancement Phase (Months 1-4)

Conceptually, we divided the CHW intervention into the following 2 phases: the enhancement phase, which consists of individualized health education, and the maintenance phase. The enhancement phase occurs during the first 4 months and includes home visits and phone calls. Although the number of home visits and phone calls is based on individualized decisions, as a rough, estimate we plan 5 home visits in this 4-month period and 2-3 phone calls per month. Although the length of calls is determined by CHW, it is expected that most calls would average under 15 minutes. In this phase, CHW helps the participant identify the issues that may affect his or her overall health and well-being. These can include direct influences, such as comorbid health conditions and behavioral risk factors, or more indirect influences, such as socioeconomic status and social context, poor health literacy, barriers in communication, and limited experience navigating the health care system. Once these barriers are identified, participants can then develop structured goals and methods for overcoming these obstacles in a manner that aligns with their needs and preferences.

CHW guides participants through this process by developing individualized health and well-being plans. This includes orienting participants on the principles of self-management and engaging them in a problem solving process that sets priorities for immediate problem resolution. To ensure that participants achieve their personal health goals regarding stroke risk and related risk factors, each CHW is tasked with a number of roles including, but not limited to, health and behavior counseling and coaching, medical service navigation (eg, scheduling appointments, sending reminders, providing guidance through the health system bureaucracy, etc), and social support (eg, identifying local social resources programs such as immigration services, tenant advocacy, and domestic violence programs). A major component of health education consists of blood pressure home self-monitoring. For participants who do not have a home blood pressure meter, CHWs help by providing one at no cost to them. However, data from these monitors will not be used for the outcome analyses. Those will be based on the blood pressure readings obtained during a structured assessment at 12 months, as described below.

Maintenance Phase (Months 4-12)

During the maintenance phase, participants are expected to independently maintain progress on their patient navigation activities and individual lifestyle intervention goals. CHWs contact participants weekly by phone to check on their progress including the status of participant action plans, updates on lifestyle modifications, and addressing new problems that may have developed. Participants also initiate contact with CHWs when in need of additional support. Phone calls are also used for patient navigation purposes including reminding participants of their next doctor's appointment and facilitating patient contact with their provider offices when needed. Home visits can also occur during this period to ensure participants are meeting their outlined goals. During the final contact, participants are notified that the intervention is concluding and that they will be contacted in the coming weeks to complete their follow-up visit at the University of Miami Clinical Research Center.

Mobile Technology Component

The mHealth component of HiSSPI intervention is led by a telehealth expert (SD) in conjunction with the external vendor, GenerationOne [44]. The vendor uses a proprietary mHealth Connect platform that is compatible with most modern cell phones (including basic cellphones and smartphones) and carrier cell phone plans. It allows for messaging through either a Web browser or using standard SMS text messages. During outreach and subsequently during informed consent, participants are made aware that if randomized to the intervention, they would have the option of also participating in the mHealth component of HiSSPI. After the initial CHW home visit, participants are asked if they wish to participate in this component of the intervention. If the participant does not have a phone and wishes to participate, CHWs assist in helping them obtain a low-cost phone such as those offered through the federal Lifeline Program (if income eligible). Participants can also designate their primary caregiver or close relative to serve as their proxy for receiving messages and providing mHealth information.

Using the mHealth Connect software (GenerationOne, Inc, Southfiled, MI, USA), we developed a set of project-specific user-friendly query routines and informational tips sent to enrolled participants on a daily basis using a 61-day looping routine. The query routines include decision branching logic that allows the system to interact with the participant based on the information they provide. Responses from participants are recorded in a clinical dashboard where CHW is able to track and follow responses and trends for their assigned patients. In addition, CHWs receive alerts if their participant answers a question out of the expected predefined normal range.

Participants can choose their preferred time to receive these daily questions.

Textbox 1. Description of Hispanic Secondary Stroke Prevention Initiative Community Health Worker training components.

University of Miami Basic Research Training:

Collaborative Institutional Initiative Training

- Human Subjects Research
- Health Information Privacy

Research Electronic Data Capture Database Software Training

Community Health Worker Certification:

500 clock hours of formal work or volunteer experience providing community health worker services in any of the following domains of practice within the last 5 years:

- Communication and Education: tasks related to community and education
- Resources: tasks related to linking community members with available health and social services
- Advocacy: tasks related to advocating for the community's health and social service needs

30 clock hours of content-specific training as follows:

- Communication and Education: 4 hours
- Resources: 4 hours
- Foundations of Health: 4 hours
- Professional Responsibility: 4 hours
- Electives (may related to any of the performance domains): 10 hours

Department of Health and Human Services Office of Minority Services:

Promotores de Salud Health Initiative: Promoting healthy choices and community changes

- Unit A: Understanding health decisions
- Unit B: Helping people make health choices
- Unit C: Understanding changes in the community
- Unit D: Health people make changes in the community

Additional training:

Florida Community Health Worker Coalition-Partnership to Train Community Health Workers in Patient-Centered Research (a 7-hour course on research training for community health workers developed with support from the Patient-Centered Outcomes Research Institute)

- Patient-centered outcomes research: rationale, definitions, role of community health workers
- Clinical trials: types, randomization
- Data collection methods: qualitative and quantitative methods, avoiding bias
- Informed consent process
- Study protocol and reporting: working in a research team
- Disseminating study results: to study participants, how community health workers can contribute to research manuscripts
- Ethics: Institutional Research Boards, privacy and confidentiality, professional boundaries

National Institutes of Health Community Health Worker Health Disparities Initiative Health Education Materials & Resources

- Su corazón, su vida: Manual del promotor y promotora de salud
- Healthy Heart, Healthy Homes series
- Salud para su Corazón: Bringing Heart Health to Latinos - A Community Program Guide for Latinos
- Approaches to Enhance Learning: Using Adult Learning and Popular Education with the National Heart, Lung, and Blood Institute Heart Health Curricula (webinar)
- Improving Heart Health with Community Health Workers, Promotores, and Community Educators (webinar)

An important component of the queries is that participants are asked to enter their blood pressure. These data are processed and organized into 3 response categories, namely, high risk (requires immediate attention, systolic blood pressure >180 mm HG), moderate risk (requires attention, systolic blood pressure >140 mm HG), and low risk or normal (systolic blood pressure <120 mm HG). These thresholds were based on existing guidelines at the time of the study [45] and clinician input (OC and JGR). For high-risk participants, the system alerts the patient to contact their physician or CHW; further, it sends the patient's name to CHW so that they are aware that the patient requires a call that same day. In consultation with project physicians (OC, JGR, SD), CHWs decide a plan of action for such participants. This may include an emergency room referral.

Participants at moderate risk are provided with automated feedback. The data also alert CHWs of participants that may require additional follow-up. This information is valuable in helping CHWs further pinpoint the areas of concern, thereby creating a more focused and effective intervention strategy; for example, this may include calling participants and asking about medication adherence or recent changes in diet. When needed, CHWs can also alert the patients' health care provider about patent blood pressure readings that remain high over several days. They can also help obtain an urgent appointment for such patients to see their primary care provider. CHWs and study team staff do not engage in medication management. When needed, they facilitate contact and interaction with the participant's primary care provider who then decides if medication changes are needed.

Training of participants in the mHealth intervention is conducted by CHWs. The training includes how to interface with the study's text support system, how to submit daily blood pressure readings, and how to use the various medication, diet, and physical activity reminders built into the system. In general, training of participants takes less than 60 minutes but varies depending on the patients' baseline level of mobile phone use. Participant caregivers are also invited to participate in the training so that they may also be able to assist in the device usage or, in some cases, become the primary user of the technology for the participant.

With respect to data privacy, users are assigned a unique name for identifying and tracking user identity, and the server does not transmit or store any identifying information. In addition, user sessions are terminated after 15 minutes of inactivity. Data within the database server are encrypted using Transparent Data Encryption, which protects data at rest and data that are being transmitted over an electronic communications network using 256-bit encryption.

Data Management

Survey data are collected on laptop computers connected to Research Electronic Data Capture [35], a secure cloud-based Web app for data capturing in both online and offline settings, managed by the University of Miami. On a monthly basis, data are reviewed by the study statistician for missing or out-of-range values and potential inconsistencies. As needed, these discrepancies are reviewed with the study team and statistician.

Sample Size and Statistical Power

We reviewed stroke and cardiovascular intervention programs to estimate the sample size required for this study [21,46]. Sample size consideration and power analyses were performed based on the primary outcome variable of systolic blood pressure. Using an SD of 21 mm HG with an alpha significance level of.05 and two-sided *t* test analyses, we estimated that 150 participants per study arm (300 participants total) could detect a minimum difference of 8 mm HG between groups with 91% power. This is smaller than the 10 mm Hg threshold in secondary stroke prevention guidelines [47]. For our secondary outcome of low-density lipoprotein), we will have 80% power to detect a minimum low-density lipoprotein difference of 13 mg/dL given SD of 39 mg/dL. For adherence to antiplatelet or antithrombotic therapy, we will have 83% power to detect a 15% difference in adherence among the intervention versus control group. All data will be analyzed using the latest SAS software (Cary, NC).

Primary Outcome

The primary outcome is a change in systolic blood pressure from baseline to the 12-month evaluation as measured using the Omron HEM-705CP automated oscillometric device (Lake Forest, IL, USA). Following the American Heart Association guidelines, 3 readings are taken, and the average of the last 2 readings is used as the blood pressure measurement [48]. The study is powered to test the hypothesis that at 1 year, systolic blood pressure of participants enrolled in the intervention will be 8 mm HG lower than those in the control (see below).

Secondary Outcomes

Secondary outcomes are low-density lipoprotein, glycated hemoglobin (for diabetic participants), and adherence to antiplatelet or antithrombotic medications (for ischemic or embolic stroke patients). To assess low-density lipoprotein and glycated hemaglobin, a certified phlebotomist obtains 10 cc of blood. Samples are spun and delivered to the University of Miami Diabetes Research Institute for lipid profiling. Glycated hemaglobin analyses are performed via latex agglutination, and low-density lipoprotein is estimated using the Friedewald equation [49]. For those with triglycerides greater than 400 mg/dl, a direct low-density lipoprotein measurement is performed. Self-reported medication adherence is assessed using the Morisky Medication Adherence Scale [50].

Confounding Variables

Potential confounders of our primary and secondary outcomes include sociodemographics (age, sex, income, and educational attainment); health insurance status; depression (Center for Epidemiological Studies Depression Scale) [51]; acculturation (modified Marin-Marin scale) [52,53]; health literacy (Short Assessment of Health Literacy-Spanish and English) validated in both English and Spanish) [54]; body mass index; and functional status (modified Rankin score) [32].

Mechanistic Variables

Mechanistically, we expect the CHW intervention to be successful in blood pressure management through 2 primary pathways. The first is through better medication management.

Although the intervention team is not involved in managing medications, our behavioral intervention can result in improved medication management through either increased medication adherence or by ensuring that patients have an appropriate and timely follow-up with their existing primary care providers who manage medications. The second is through lifestyle changes, primarily diet and exercise.

To conduct potential exploratory analyses of how the intervention may have resulted in improved outcomes, we are collecting data on potential mediators including medication adherence, medication intensification, salt intake, physical activity, and provider visits. This will allow us to examine the degree to which any improvements in blood pressure were mediated by changes in these variables. We are also collecting detailed data on service intensity. We can then examine the correlations between blood pressure control and items such as number of home visits, telephone calls, and group visit participation. Similarly, items in the cell phone intervention can also be correlated with blood pressure control, such as the number of days in which blood pressure values were uploaded or frequency of SMS text messaging responses. A summary of variables being collected is shown in Table 1.

Statistical Analysis

The distribution of baseline values and outcomes will be examined for each arm. The intervention effects on outcomes (systolic blood pressure, low-density lipoprotein, and glycated hemaglobin) will be evaluated using linear regression models for continuous variables as a function of intervention status as well as with categorical classification variables to index time intervals pre- and postintervention. We will use statistical tests of the estimates of the regression parameters from this model to compare the major outcomes before and after the intervention groups in the full sample as well as between intervention groups. Adherence to antiplatelet or antithrombotic therapy will also be evaluated using logistic regression models as a function of intervention status. Covariates that will be included in the models will include age, sex, body mass index, and educational attainment. Relationships between the outcome variables and other potential covariates such as income, health insurance status, health literacy, and functional status will be explored to determine their potential inclusion in final models.

Table 1. List of variables and measures included in Hispanic Secondary Stroke Prevention Initiative baseline survey.

Variables	Measures or methods
Primary outcomes	
Blood pressure [48]	OMRON HEM-705CP, validated oscillometric device
Secondary outcomes	
Low-density lipoprotein [49]	Roche Cobas c501 (Friedewald equation), also registry
Glycated hemaglobin	Bio-Rad D-10 Latex agglutination, also from registry
Adherence to antiplatelet or antithrombotic medication [50]	Medication Adherence Scale
Exploratory outcomes	
Quality of life [55,56]	EuroQual (NINDS CDE[a] core)
Visits to providers	Agency for Healthcare Research and Quality Medical Expenditure Panel Survey
Hospitalization or stroke admissions [57]	Medical Expedinture Panel Survey and Northern Manhattan Study Questions
Mechanistic variables (mediators)	
Blood Pressure Behaviors Compliance [58]	Hill Bone Scale (salt intake & blood pressure medication adherence)
Fruit and Vegetable Intake [59]	Behavioral Risk Factor Surveillance System (as a very rough marker of any diet change)
Medication Intensification [20]	Miami Healthy Heart Initiative Medication Intensification Criteria
Physical Activity [60]	International Physical Activity Questionnaire, Common Data Elements
Covariates (moderators)	
Sociodemographics	NINDS CDE (core)
Acculturation [53]	Marin-Marin (5 items)
Health Literacy [54]	Short Assessment of Health Literacy-Spanish and English
Depression [51]	Center for Epidemiologic Studies Depression (NINDS CDE core)
Body mass index	Genentech Stadiometer, Platform Scale
Functional status [32,33]	Modified Rankin Scale (NINDS CDE core)

[a]NINDS CDE: National Institute of Neurological Disorders and Stroke Common Data Elements.

Results

Funding for the study began on 2014 and the first participant was enrolled on February 26, 2015. Enrollment is planned to be completed by 2018, and a manuscript describing the baseline characteristics of the population is expected to be completed by 2019 and submitted for publication in 2020.

Discussion

Limitations

Study attrition is a concern. In a prior diabetes study, we experienced 21% attrition [21]. As Figure 1 shows, even with such attrition, we would have >80% power to detect an systolic blood pressure difference of 8 mm HG. However, in that study, patients were younger and a much more geographically mobile group than stroke survivors. Thus, for HiSSPI, we expect an attrition rate of about 10%. Analytically, attrition will be handled by examining baseline characteristics of completers and noncompleters and testing patterns of attrition for randomness or ignorability. If the pattern of missing data is nonignorable, 1 approach is using baseline values carried forward. However, baseline values carried forward may not be the best method, and sensitivity analyses will be considered using different approaches such as weighted generalized estimating equations (using the inverse probability of dropout), multiple imputation, and propensity scores [61,62].

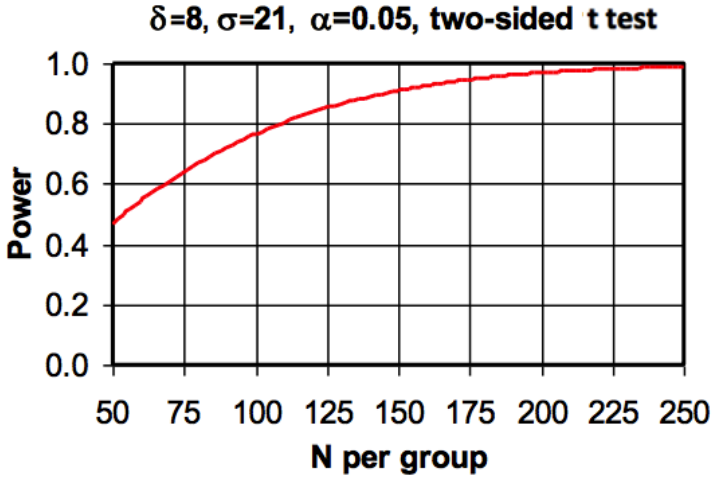
As noted above, Miami has a diverse Latino population of Caribbean, Central, and South Americans facing numerous distinct barriers to quality stroke care. Thus, it is an ideal location to generate findings that generalize to the US Latino population. In addition, initially, we also considered having Puerto Rico as another recruitment site. This site would allow us to test the intervention in a more homogenous Latino population where barriers such as immigration status and language are mitigated. Unfortunately, budgetary constraints did not allow us to include this site.

Lastly, a gap in the CHW literature is that few studies model the costs and benefits of CHW programs. Our proposed intervention of having one CHW assigned to a panel of 25-30 patients is costs approximately US $2000 per patient. Even though this figure pales in comparison with the cost of a subsequent stroke, of key importance to policy makers would be a formal cost-effective analysis. Although a formal cost-effective analysis is not part of the protocol, as part of the survey instrument, we will be collecting quality of life data using a standardized health state instrument (EQ5) and collecting data on health care utilization and hospitalizations. If linked to expenditure data, such data would allow for a future cost-effective evaluation.

Conclusions

Results collected from HiSSPI will provide important information on the effectiveness of a combined CHW and mHealth intervention on recurrent stroke risk among Hispanic-Latino populations. The study highlights the innovative role CHWs play in chronic care delivery, and our findings will further gauge the feasibility of this framework in the existing health care system using mobile technologies, which may be more scalable options for chronic disease management.

Figure 1. Statistical power and least detectable differences in Hispanic Secondary Stroke Prevention Initiative for systolic blood pressure.



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Conflicts of Interest

None declared.

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Abbreviations

CHW: community health worker
HiSSPI: Hispanic Secondary Stroke Prevention Initiative
NINDS CDE: National Institute of Neurological Disorders and Stroke Common Data Elements
SMS: short message service
UHealth: University of Miami Health System

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Protocol

Mind-Body Treatment for International English-Speaking Adults With Neurofibromatosis via Live Videoconferencing: Protocol for a Single-Blind Randomized Controlled Trial

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Abstract

Background: Neurofibromatoses (NF) are rare genetic conditions associated with substantial psychosocial burden and impaired quality of life (QoL). We developed the first NF-tailored mind-body program (the Relaxation Response Resiliency Program for NF) and adapted it for delivery via live videoconferencing to decrease participation barriers and increase its reach. In a pilot randomized controlled trial (RCT), we found that the Relaxation Response Resiliency Program for NF had excellent feasibility and acceptability when delivered via live videoconferencing; furthermore, the Relaxation Response Resiliency Program for NF showed proof of concept in improving QoL compared with an NF-tailored health education control program (the Health Enhancement Program for NF). A fully powered trial is needed to ascertain the efficacy and durability of the Relaxation Response Resiliency Program for NF delivered via secure live videoconferencing among geographically diverse patients.

Objective: The objective of this study is to evaluate the efficacy of the Relaxation Response Resiliency Program for NF versus the Health Enhancement Program for NF, both delivered in groups via secure live videoconferencing, among geographically diverse patients with NF across the United States and internationally. Here we describe the protocol, manualized treatments, evaluation plan, and study design.

Methods: This is a single-blind RCT. Patients are told that they will be randomized to one of the two stress management programs (stress management program 1: the Relaxation Response Resiliency Program for NF and stress management program 2: the Health Enhancement Program for NF). Patients are recruited from NF-specific national and international foundations and NF clinics across the United States through study ads and a video of participants who have completed the program as part of the pilot study or ongoing trial. Interested participants are screened for eligibility via secure live videoconferencing (self-reported stress and difficulties coping, no change in antidepressant medication within the past 3 months, no psychotherapy within the past 3 months, no major upcoming surgeries within the next 12 months, English speaking, and able to complete questionnaires online and participate in live video interventions) and consent obtained before participation. Both programs are manualized comprising 8 sessions delivered via secure live videoconferencing by trained clinical psychologists. Primary outcomes are physical health QoL and psychological health QoL. Secondary outcomes are social relationship QoL, environment QoL, and psychosocial and resiliency variables. Outcomes are assessed at baseline, posttraining, and 6- and 12-month follow-ups.

Results: The trial is ongoing. Thus far, we have recruited 55 patients and aim to recruit a total of 224. Recruitment will close in May 2020; we plan to complete data analyses by June 2021.

Conclusions: This trial will answer key questions about the efficacy and durability of the Relaxation Response Resiliency Program for NF via live videoconferencing with English-speaking adults with NF worldwide. If found efficacious, this program can be readily implemented through national and international NF foundations and NF-specific clinics. The virtual model of delivery has extensive applications for patients in rural areas, those with disability or illness that precludes travel to clinics, and those with rare diseases.

Trial Registration: ClinicalTrials.gov NCT03406208; https://clinicaltrials.gov/ct2/show/NCT03406208 (Archived by WebCite at http://www.webcitation.org/72ZoTDQ6h)

International Registered Report Identifier (IRRID): RR1-10.2196/11008

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KEYWORDS

neurofibromatosis; quality of life; stress management; mind-body; videoconferencing; resiliency; mobile phone

Introduction

Neurofibromatoses (NF) are the most common genetic neurological conditions worldwide and affect men and women of all races and ethnic groups [1,2]. NF comprises 3 genetically distinct conditions (NF1, NF2, and Schwannomatosis) unified by the predisposition to nerve sheath tumors that tend to be histologically benign. Each NF type has characteristic symptoms: NF1 is typically associated with disfiguring cutaneous tumors [3,4]; NF2 is associated with hearing loss, facial weakness, and poor gait [5]; and Schwannomatosis is associated with chronic disabling pain [6]. There is no cure for NF; treatment is limited to symptom management through surgical and palliative means [7].

Despite their distinct pathophysiology, patients' psychosocial profile is similar regardless of the NF type [8]. As a group, patients with NF have lower quality of life (QoL) and experience more pain compared with general population norms [8,9]. Moreover, rates of depression, anxiety, and stress among patients with NF are comparable to those among patients with cancer and coronary heart disease [9,10]. Despite this heavy psychological burden, there are no evidence-based psychosocial treatments that directly address the specific needs of this population.

We developed the first psychosocial treatment designed to meet the specific needs of patients with NF using a group format. Using a sequential approach that included focus group discussions; in-person open-pilot testing with exit interviews (ie, semistructured interviews conducted by the study therapist after the participants completed the program); and a preliminary randomized controlled trial (RCT) [11], we adapted an evidence-based mind-body intervention [12] to the specific needs of patients with NF and for live video delivery. The transition from in-person to live videoconferencing delivery was done based on feedback from patients about the burden of traveling for weekly visits in order to increase feasibility and to extend our reach to patients across the United States and internationally. In our pilot RCT [11], we showed that 3RP-NF is highly feasible and acceptable when delivered via live videoconferencing. Moreover, we showed that participation in 3RP-NF resulted in greater sustained improvement in QoL, psychosocial functioning [11], and resiliency variables [13] compared with an active control program (the Health Enhancement Program for Neurofibromatosis [HEP-NF]) [14], which was also delivered via videoconferencing using a group format.

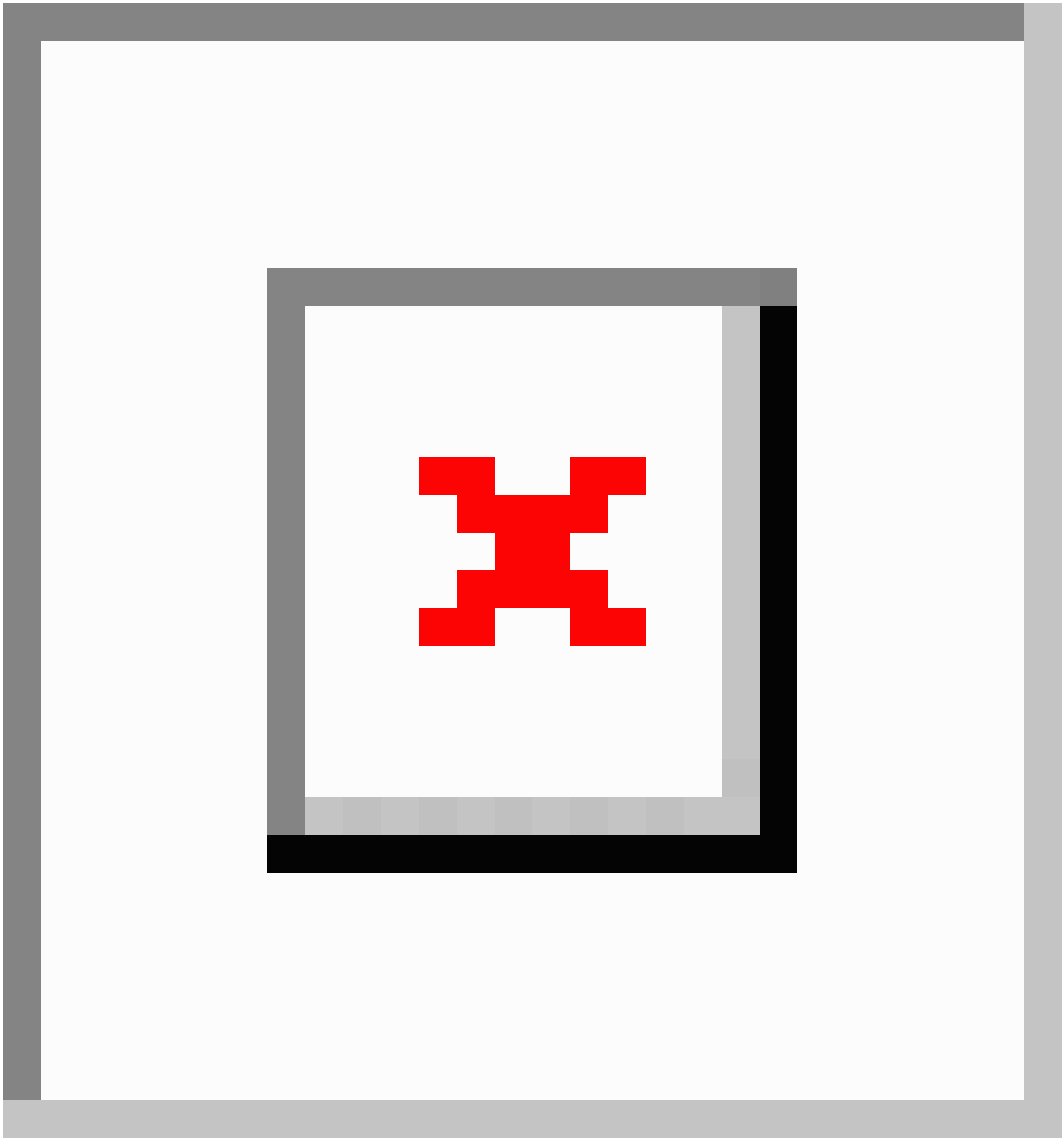
We are now conducting the first fully powered efficacy RCT in adults with NF (N=224). The primary aim of this study is to determine the efficacy and durability of 3RP-NF versus HEP-NF regarding the coprimary outcomes of physical health QoL and psychological health QoL. Secondary outcomes include social relationship QoL, environment QoL, and psychosocial and resiliency measures. We hypothesize that 3RP-NF will be more efficacious compared with HEP-NF in improving coprimary and secondary outcomes from baseline to the end of active training and that the benefits of 3RP-NF participation will be maintained at 6- and 12-month follow-ups. The secondary aim is to examine the degree to which treatment-dependent changes in the coprimary outcomes are mediated by improvements in depression, anxiety, pain intensity, pain interference, social support, gratitude, optimism, mindfulness, empathy, coping ability, and stress (conceptual mediators) and modified by NF type, age, race, ethnicity, learning disability, and education level. We also plan to ascertain the minimal clinically important difference (MCID) for QoL variables for NF from baseline to posttraining, baseline to 6 months, and baseline to 12 months. This paper describes the study protocol.

Methods

Study Design

This is an ongoing, single-blind RCT of the efficacy and durability of 3RP-NF versus HEP-NF in improving QoL and psychosocial functioning in adults with NF1, NF2, and Schwannomatosis. Both programs are delivered via secure live videoconferencing, which allows enrollment of English-speaking participants across the United States and internationally. To maintain the single-blind design, we refer to the 3RP-NF and HEP-NF as Stress Management Programs 1 and 2 (SMP1 and SMP2, respectively) in all study materials. We began enrolling participants in September 2017. A flowchart of the study design is presented in Figure 1.

Figure 1. Study design. SMP: stress management program.



Textbox 1. Study inclusion criteria.

Participants fulfilling the following requirements are included:

- Those with a diagnosis of neurofibromatosis (NF)1, NF2, or Schwannomatosis
- Those aged ≥18 years
- Those capable of completing and fully understanding the informed consent process, study procedures, and assessments in English
- Those with at least a 6th grade self-reported reading level
- Those with self-reported difficulties coping with NF symptoms
- Those scoring 6 or higher on the Perceived Stress Scale 4-item

Textbox 2. Study exclusion criteria.

Participants in any of the following categories are excluded:

- Those with a major medical comorbidity, which is not related to neurofibromatosis (NF) and expected to worsen within the next 12 months
- Those with a recent change in antidepressant medication (within the past 3 months)
- Those with recent participation in cognitive behavioral or relaxation therapy (within the past 3 months)
- Those with a significant mental health diagnosis requiring immediate treatment (eg, untreated bipolar disorder, psychotic disorder, and active substance dependence) obtained via self-report and observation during prescreening
- Those unable or unwilling to complete assessments electronically via Research Electronic Data Capture
- Those unable or unwilling to participate in group videoconferencing sessions

Setting

This study is being conducted in a large academic medical center in the northeast region of the United States. The use of virtual recruitment and live videoconferencing for intervention delivery allows participants from the United States and internationally to engage in the study from the comfort of their own homes or any location with internet access. Participants are recruited through the NF Registry at the Children's Tumor Foundation (CTF), which has over 7000 members in the United States and internationally, various NF groups and clinics across the United States, and international NF centers (eg, England and Australia).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are detailed in Textboxes 1 and 2, respectively. The criteria were selected based on the guidelines for psychosocial treatment development [15] and for bridging efficacy with effectiveness [16]. These criteria were meant to be as inclusive as possible to maximize reach and uptake while reducing potential study confounders. Consistent with prior research that has utilized the Perceived Stress Scale 4-item[17] (PSS-4) measure as a screening tool for elevated stress, the potential participants are required to score at least 6 on PSS-4 [18,19]. Screening is conducted via secure live videoconferencing.

Recruitment

Our institutional review board (IRB)-approved study advertisement is distributed electronically (eg, email listserv) and on paper through the CTF registry, national and international NF organizations, NF social media groups, and at NF clinics across the world. In addition, an IRB-approved recruitment video with snippets of patients' experiences with study participation was created and disseminated at NF patient forums and on the official website of CTF. Potential participants send emails to our study coordinator who responds within 24 hours using a scripted email describing the study and offering the potential participants the opportunity to schedule a live videoconference screening with study staff. The study coordinator attaches the informed consent to the email to provide individuals time to review the study procedures, but instructs the potential participants not to sign the consent form before the screening appointment. The potential participants are provided 2 days after the initial email contact to respond before the study coordinator sends a follow-up email. The study coordinator stops contacting the potential participants after three unanswered emails.

Vidyo Software Installation

All study appointments are conducted using the secure, Health Insurance Portability and Accountability Act (HIPAA)-approved live videoconferencing software Vidyo, which is a user-friendly platform used clinically at our academic medical center. Prior to the screening appointment, potential participants receive instructions via email to download, install, and access Vidyo on their personal, webcam-equipped, internet-connected devices (eg, laptop, desktop computers, and tablets). Participants are informed that devices with screens that are as large as possible are preferred to provide them with the best video-viewing experience. However, to increase generalizability and reach, participants who do not own compatible computers or tablets are allowed to use smartphones if necessary. The study coordinator also offers telephone appointments to assist potential participants with software installation and configuration (eg, ensuring the software is granted access to microphones and webcams) as needed.

Technical Considerations

Participants have different levels of experience using technology and many have NF-related learning disabilities. These issues present several challenges in installing and configuring the videoconferencing software. First, when using a tablet or smartphone, the software must be downloaded as an "app" acquired through an app distribution platform (eg, app store or Google play store), which requires the user to have and access their own accounts. Users who are unfamiliar with "app stores" may require assistance creating or accessing an account and initiating an app download and installation. Second, the Vidyo software is designed to autodetect speakers, microphones, and webcams installed on the device. However, in instances where the device has multiple forms of hardware installed or where autodetection is unsuccessful, the study coordinator may need to assist patients in software configuration. Third, different types of operating systems (eg, Mac OS X, Microsoft Windows) have slight variations regarding the installation and configuration process as well as the user interface. The study coordinator has undergone extensive training to be able to assist participants with various technical challenges to ensure that all participants are provided the opportunity to enroll regardless of their prior experience using technology. The coordinator has also received specific training on how to interact with potential participants

who might feel intimidated by the technological aspect of the project to make them feel comfortable and at ease. Furthermore, the team has prepared simple, easy-to-use, step-by-step instructions that are distributed to participants.

Screening and Enrollment

After the potential participants have successfully installed Vidyo, the study coordinator schedules a virtual screening appointment during which the study staff determines eligibility and performs the informed consent process. Eligibility is determined based on the inclusion and exclusion criteria presented in Textboxes 1 and 2, respectively. All eligible participants are provided with an overview of the study procedures. The study therapist ensures that potential participants have a thorough understanding of the study procedures and are comfortable with the program format. The potential participants are encouraged to ask any questions about the informed consent document and study procedures, and the study therapist answers all study-related questions before informed consent is obtained. Eligible individuals who agree to participate are scheduled for the next available group (stratified by NF type) and are provided with instructions for returning the signed consent form to the study coordinator electronically (ie, via email or fax). Our IRB considers participants to be enrolled in the study when they return the informed consent document.

Scheduling Considerations

The use of secure live videoconferencing allows participants to access the group session wherever they have a reliable internet connection and privacy. Thus, both participants and study therapists have flexibility in scheduling by having the option to access the treatment from home or office if privacy and internet needs are met. The ability to enroll geographically diverse participants is a strength of the current protocol. However, geographic diversity, which spans time zones across the globe, and an individual randomization schedule (see the subsequent section on randomization) pose challenges to scheduling that are addressed as follows: First, each pair of treatment groups (ie, 3RP-NF and HEP-NF) is facilitated consecutively within a 3-hour window (ie, 90 minutes per group) by a single study therapist; please see the "Randomization Considerations" section for details. Participant availability is required for the full 3-hour window to ensure that the participant is able to attend either group to which he or she is randomized. Second, we assess a wide range of participant availability, including during nights and weekends, to find a common time that will accommodate the study therapist's schedule and as many participants as possible.

Assignment to Treatment Arm

Participants are randomly assigned in a 1:1 ratio to either the 3RP-NF or the HEP-NF group via a permuted-block randomization (random blocks of 2 and 4), stratified by diagnosis (NF1, NF2, or Schwannomatosis), using a computer-generated (ie, SAS version 9.4; SAS Institute Inc, Cary, NC, USA) randomization schedule developed by our biostatistician. Randomization occurs individually for each participant after baseline assessments have been completed. After randomization, the study coordinator emails each participant to inform them of their assigned group and confirms when their group will meet within the original 3-hour window (ie, within the first 90 minutes or the last 90 minutes). To maintain blinding, participants are simply told whether they have been randomly assigned to SMP1 or SMP2. The study is single-blinded; thus, only participants are concealed of their group allocation.

Randomization Considerations

Multiple randomization methods are available to assign participants to treatment arms within an RCT, including individual and cluster randomizations. We considered a cluster randomized design to facilitate scheduling feasibility, requiring participants to be available for only a 90-minute window and then randomizing that time slot to a treatment condition. However, given that our unit of inference is at the individual level and that cluster randomization can reduce statistical power [20], we selected an individual randomization schedule while considering the scheduling needs of participants, such as evening group times to accommodate working individuals. We also considered block randomization that would allow us to assign even numbers of participants to each pair of treatment groups. The current permuted-block design has considerable statistical and experimental design advantages that prevent the study team from deducing the next possible assignment. Due to limitations in the Vidyo software, we are unable to accommodate more than 8 participants in a single group. As we assign participants to a 3-hour block and then randomize them to treatment condition, we could ensure equal groups (ie, 8 per group) by using blocks of 16 for each time slot. However, that would allow the study team to deduce the final allocation before randomization. Thus, we decided to randomize patients in a permuted-block design, accepting the potential for uneven groups. Once a group has reached 8 participants, randomization for that full 3-hour time block is closed so as not to risk randomizing a 9th participant to a full group. While this can result in uneven groups (eg, 8 participants in one group and 6 in another), the integrity of the randomization schedule is maintained, and it has been feasible in our design to date.

Treatment Conditions

Both treatment conditions include 8 weekly 90-minute group sessions delivered via secure live videoconferencing. Sessions are delivered on the same day and time each week for 8 consecutive weeks. Both treatments follow respective patient manuals, which are emailed as PDF documents to participants 2 days prior to their first session. The patient manuals are designed for a 6th grade reading and comprehension level. To further accommodate learning disabilities or other cognitive difficulties, participants are asked to bring the manual with them during each treatment session, either electronically or in print, to follow along and take notes during the session. A paper copy is mailed to participants who are not comfortable using the manual electronically and are unable to print the manual.

Each week, participants receive a reminder email on the day of their group session with instructions for logging into the Vidyo software. They are asked to email or call the study coordinator if they experience any technical difficulties and to email their

study therapist if they are not able to attend the session. Moreover, participants who do not log into the session within 15 minutes of the start time receive a phone call from the study coordinator to inquire whether they are having technical difficulties and whether they will be able to attend the session. The study coordinator is available for the duration of each group session, and in the event of technical difficulties, he or she assists participants in real-time troubleshooting with the goal of enabling participants to log into the session as quickly as possible.

Relaxation Response Resiliency Program for Neurofibromatosis

The 3RP-NF is a comprehensive, multimodal treatment program designed to improve the ability to cope with NF symptoms and stress. The program retains the main components and structure of the parent program, which combines the elicitation of the relaxation response (RR) with cognitive behavioral theory and the evolving field of positive psychology [12,21-28]. 3RP has three core components: (1) RR elicitation strategies to help decrease the stress response associated with NF symptoms and general life stress (eg, mindfulness skills, meditations, guided imagery, body scan); (2) stress and medical symptom appraisal and coping to help patients understand the interrelations among thoughts, behaviors, feelings, and sensations and learn adapting coping skills (eg, cognitive restructuring, problem solving, activity scheduling); and (3) growth enhancement or positive psychology skills that help patients experience pleasure and gratitude and engage in prosocial and empathic behaviors (eg, appreciations, use of humor, empathic communication). All skills have been modified to specifically address NF concerns identified through focus group discussions and exit interviews (ie, semistructured interviews conducted by the study therapist after participants completed the program) during 3RP-NF development process. Skills are taught using NF examples. The program also provides educational information on nutrition, exercise, and sleep hygiene.

Videoconferencing sessions consist of the study therapist and up to 8 participants, who can see each other but can block their video if desired. Each session begins with setting an agenda and a review of the material from all previous sessions. Each session introduces at least one RR skill and an additional cognitive behavioral or positive psychology skill, with presentation of NF-specific examples. The study therapist leads in-session exercises to demonstrate each skill and assigns home practice of the skills to facilitate mastery. In-session practice and review of all the skills taught in prior sessions is unique to the 3RP-NF and done to compensate for the high rates of cognitive and learning disabilities in the NF population. Before each session, participants receive an MP3 file recording with the particular RR skill that will be taught and practiced during the particular group session to aid with home practice. Between sessions, participants are asked to practice the skills daily, complete a home practice log, and email it to the study therapist at least 2 hours before the start of each group session to provide enough time for the study therapist to review each participant's practice. Home practice includes three core elements: (1) setting 1 weekly goal; (2) practicing an RR skill, starting with 5 minutes daily for the first week and gradually increasing the length, frequency, or both of practice throughout the 8-week program; and (3) writing down 1-3 appreciation statements daily. Each session includes a review of home practice, including problem solving of barriers as needed, with specific feedback from patients. A complete description of treatment content by session is presented in Table 1.

Table 1. Outline of the Relaxation Response Resiliency Program for Neurofibromatosis.

Session	Topics	Skills
Symptom management, stress management, and resiliency training	1. Stress response 2. Relaxation response 3. Resiliency 4. Mind-body connection	• Single-pointed focus meditation • Energy battery • Specific, Measurable, Attainable, Realistic, and Time-based (SMART) goals • Gratitude and appreciations
The relaxation response	1. Developing routines for consistent skill practice 2. Recuperative sleep 3. Relaxation response and emotions	• Body scan • Diaphragmatic breathing • Sleep hygiene • Identifying emotions and physical sensations
Stress and symptom awareness for patients with neurofibromatosis (NF)	1. Mindful awareness 2. Stress awareness 3. Social support	• Mindful awareness meditations (eg, mindful eating) • Identifying stress warning signals • The social support diagram
Mending the mind and body of patients with NF	1. Movement to elicit the relaxation response 2. Negative automatic thoughts (NATS) 3. Thought distortions	• Stretching and chair yoga for relaxation • Adaptive thinking: identifying NATS and thought distortions • Pleasant experiences to build resiliency
Creating an adaptive perspective	1. Adaptive thinking 2. Healthy eating	• Generating adaptive thoughts through reframing, use of positive emotions or beliefs, and acceptance • Stop, breathe, reflect, choose • Guided imagery • Food pyramid
Promoting positivity	1. Positive psychology 2. Optimistic explanatory style 3. Physical activity	• Loving kindness meditation • Telling our stories with optimism • Identifying relaxation signals • Guidelines for health activity levels
Healing states of the mind	1. Empathy toward self and others 2. Choosing appropriate coping strategies 3. Acceptance	• Contemplation • Problem-solving and acceptance strategies • Coping decision tree • Mindful awareness • Letter to self
Humor, empathy, and staying resilient	1. Staying resilient 2. Humor	• Idealized self-imagery • Laughter in daily life • SMART goals for continued skill practice

The Health Enhancement Program for Neurofibromatosis

The parent Health Enhancement Program (HEP) [14] is a group-based health education program that addresses multiple domains of healthy living that are known to impact stress management, including sleep, diet, and physical activity. The HEP-NF has been adapted to address the specific needs of patients with NF, including educational information on NF-specific stressors and medical symptoms, NF-specific barriers to healthy lifestyle behaviors (eg, appearance concerns, pain), self-management of medical care, and navigating the medical system. Adaptations were made using educational materials from the CTF website, research literature on NF, and information from focus group discussions. The program does not teach any of the 3RP-NF skills.

As with the 3RP-NF sessions, each HEP-NF session is composed of the study therapist and up to 8 participants who are present in a shared videoconferencing meeting. Each session of the HEP-NF begins with setting an agenda and review of previous material. The study therapist presents educational information on the session topic and invites participants to provide examples from their own experiences. Participants are encouraged to pick a lifestyle skill learned in-session for use between sessions. A complete outline of content by session is presented in Table 2.

Treatment Fidelity

We use guidelines established by the NIH Behavior Change Consortium to monitor 5 areas of treatment fidelity:

- Design
- Training
- Treatment delivery
- Receipt of treatment
- Enactment of treatment skills

Table 2. Outline of the Health Enhancement Program for Neurofibromatosis.

Session	Topics	Skills
Connection between physical and mental health	1. Stress and mental health 2. Stress and physical illness 3. Connection between lifestyle behaviors and physical and emotional health	• Knowledge of lifestyle behaviors • Goal setting
Neurofibromatosis (NF) and stress	1. Types of NF 2. Stress associated with each NF type	• Identifying personal NF stressors • Identifying shared stressors among NF types • Goal setting
Sleep and wellness	1. Sleep and physical and emotional well-being 2. Sleep system (eg, circadian rhythm) 3. Behavioral patterns and sleep	• Sleep hygiene • Stimulus control • Checklist for better sleep
Exercise and wellness	1. Physical activity recommendations 2. Maintaining a healthy weight	• Identifying current activity patterns • Identifying and problem solving barriers to activity • Goal setting
Nutrition		
Basic information	1. Food groups and portion sizes 2. Calories and nutrient density	• Reading and understanding nutrition labels • My healthy plate guidelines • Visualizing portion size
Healthy weight and weight loss	1. Healthier meals and snacks 2. Eating out healthy 3. Weight and health 4. Healthy weight loss	• Preparing a shopping list • Tips for eating out • Calculating body mass index
Managing health care	1. Communicating with health care providers 2. Preparing for a medical visit 3. Medication adherence	• Maintaining up to date records (eg, lists of doctors, medications, recent tests) • Health diaries • Role plays of preparing and asking questions of medical providers • Tips for managing medications
Review	1. Review of healthy sleep 2. Review of physical activity 3. Review of nutrition 4. Review of NF and stress 5. Review of health care management	• N/A[a]

[a]N/A: not applicable.

Design

All study staff attends weekly team meetings to monitor and record participant progression through the study, including treatment "dose" (eg, session attendance, out-of-session contact with therapists) and any deviations from the prescribed dose. In addition, the study coordinator and project director meet individually each week to review progress and upcoming tasks. The principal investigator (PI) participates in weekly meetings and conducts quality control checks on a monthly basis.

Training

All study therapists are advanced graduate students or PhD-level clinical psychologists with experience in mind-body therapy. Each study therapist attends the 8-week parent program 3RP, led by a seasoned clinician at our academic medical center, as a participant observer. The study therapists also undergo study-specific training including learning general information about NF; watching videos of patients with NF1, NF2, or Schwannomatosis who are describing their symptoms; and specific training on the adaptation and delivery of skills to patients with NF. The therapists receive training about the importance of adherence to the treatment manual and completion of study-related forms. The study therapists attend weekly in-person group supervision to assure adherence to the protocol, discussion of specific patient concerns (eg, home practice challenges), and review of upcoming group sessions.

Treatment Delivery

All study therapists deliver session content according to the respective patient manuals and complete adherence checklists after each session. The adherence checklists are reviewed by the PI weekly during clinical supervision. Furthermore, all study sessions are audiorecorded, and 15% are randomly selected to be reviewed for adherence.

Receipt of Treatment

The study therapists monitor and support patients' ability to comprehend and utilize treatment by reviewing previous content and setting an agenda at the start of each session. The study therapists elicit feedback from patients about their comprehension, goals, motivation, and use of skills throughout each session as new material is taught. Participants are instructed to follow along and take notes in their treatment manual, and to review the manual out of session, to facilitate comprehension.

Enactment of Treatment Skills

Participants are instructed to set weekly goals for applying skills and information presented in each session. The study therapists review home practice and problem solve barriers weekly.

Considerations for Participant Safety During a Virtually Delivered Program

The safety of participants is evaluated at multiple study points. At the time of enrollment, participants are asked to provide the names and phone numbers of two family members or friends who could be contacted in case of emergency or if study staff has concerns about a participant's safety (eg, inability to contact participant following endorsement of suicidal ideation). At baseline, participants complete a measure of depressive symptomatology, which asks about the frequency of "Thoughts that you would be better off dead or of hurting yourself in some way." If participants provide any endorsement (ie, any response greater than "not at all") to this item, the electronic data capture system automatically emails the study coordinator, project director, and PI. The study coordinator and project director communicate with the PI to provide patient contact and emergency contact information if needed. The PI, a licensed clinical psychologist, immediately contacts the participant via phone to conduct a suicide risk assessment, including the development of a safety plan and determination of need for higher level of care. If the PI is unable to contact the study participant within 24 hours, the PI then calls the patient's individual emergency contacts to locate the participant and assess safety. The safety of participants is always prioritized over study participation. Participants who are determined to need a higher level of care or refuse to comply with safety procedures (eg, refuse to conduct a risk assessment over the telephone) are removed from the study and provided with information about resources for care as appropriate. Participants who are determined to be at low suicide risk and appropriate for continuation in the study are monitored by the study therapists and discussed during weekly clinical supervision. At follow-up, the same procedures for risk assessment and referral to higher levels of care, as needed, are followed.

Assessments

Participants complete assessments online through the secure Web app, Research Electronic Data Capture (REDCap) [29]. Baseline assessments are completed after obtaining informed consent, prior to randomization, and no more than 2 weeks prior to the first group session. Posttraining assessments are emailed to participants within 24 hours of the final group session. Participants who have not completed the posttraining assessments within 3 days receive a reminder email from the study coordinator and a phone call from the study therapist. The study therapists contacts the remaining participants daily (via phone or email as appropriate) to facilitate the completion of assessments within 1 week of the final group session. Furthermore, 6- and 12-month follow-up surveys are emailed to participants 1 week before the respective assessment due date. Participants who do not complete the questionnaires within that week then receive three additional email reminders and up to three phone calls from the study therapist or PI. The study staff ceases attempt to obtain 6-month follow-up after 2 months (ie, month 8). Participants who do not complete the 6-month follow-up are contacted as usual to complete the 12-month assessment. Participants who do not complete the 12-month follow-up after 2 months (ie, month 14) are considered lost to follow-up, and their participation in the study is terminated. Each assessment is completed at each time point unless otherwise specified.

Sociodemographic Information

Gender, age, race, ethnicity, marital status, NF type, presence of a learning disability (self-report), and education level (number of years in school) are collected using a demographic questionnaire. This assessment is only delivered at baseline.

Primary Outcomes: Physical Health Quality of Life and Psychological Health Quality of Life

The World Health Organization Quality of Life Brief version (WHOQOL-BREF) [30] is a 26-item self-report survey used to measure four domains of QoL: physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items). The physical health QoL and psychological health QoL domains are the coprimary outcomes of this study. The physical health domain assesses an individual's ability to participate in activities of daily living and his or her dependence on medicinal treatments and medical aids for daily functioning, energy and fatigue, mobility, pain and discomfort, sleep and rest, and work capacity. The psychological health domain assesses satisfaction with bodily image, frequency of negative and positive emotions, self-esteem, spirituality, and ability to concentrate. Scores are reported as transformed domain scores (0-100), with high scores depicting a greater QoL. No NF-specific MCID has been established for the WHOQOL-BREF; however, a 6.25-unit improvement has been extrapolated from the MCID for patients with cancer available for the parent scale WHOQOL-100. Thus, a 6.25-unit increase is used as an indicator of clinically meaningful improvement in physical health QoL and psychological health QoL in the current study.

Secondary Outcomes: Social Relationship Quality of Life and Environment Quality of Life

The social relationship QoL and environment QoL domains of the WHOQOL-BREF are secondary outcomes of this study. The social relationship domain assesses satisfaction with personal relationships, availability of social support, and satisfaction with sexual relationships. The environmental health domain assesses perceived financial resources, physical safety and security, accessibility and quality of health care and social services, home environment, opportunities for learning and

growth, opportunities for recreation and leisure activities, physical environment (pollution, noise, climate, traffic), and transportation. The domains are scored in accordance with the instructions mentioned above.

Conceptual Mediators

Depression

The Patient Health Questionnaire 9-Item version [31] is a self-report survey used to measure the frequency of depression symptoms (eg, little interest or pleasure in doing things, trouble falling or staying asleep, poor appetite or overeating, trouble concentrating) over the past 2 weeks. Responses are formatted as a 4-point Likert scale ranging from 0 ("Not at All") to 3 ("Nearly Every Day"). The items are summed to generate a total score, with higher scores indicating greater severity of depression symptoms.

Anxiety

The Generalized Anxiety Disorder 7-Item version [32] is a self-report survey used to measure the frequency of anxiety symptoms (eg, feeling nervous or on edge, not being able to stop or control worrying, being restless, becoming easily annoyed or irritable) over the last 2 weeks. Responses are formatted as a 4-point Likert scale ranging from 0 ("Not at All") to 3 ("Nearly Every Day"). The items are summed to generate a total score, and higher scores indicate greater severity of anxiety symptoms.

Pain Intensity

The characteristic pain intensity subscale of the Graded Chronic Pain Scale [33] uses three separate 11-point numerical rating scales ("0 = no pain" to "10 = pain as bad as it could be") to assess current momentary pain, worst pain, and average pain over the previous week.

Pain Interference

The PROMIS Pain Interference version Short Form 8a [34] is an 8-item self-report survey used to measure the extent to which pain interferes with activities of daily living, including household chores, work, and social activities, over the past 7 days. Responses are formatted as a 5-point Likert scale ranging from 1 ("Not at All") to 5 ("Very Much"). The items are summed to generate a total score and cross-referenced with the score conversion table to translate the raw score to a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a SD of 10. Therefore, an individual with a T-score of 40 is 1 SD below the mean.

Stress

The Perceived Stress Scale 10-Item version [35,36] is a self-report survey that assesses the frequency of thoughts or feelings related to stress (eg, becoming upset with something unexpected, feeling unable to control important things in life, and feeling incapable of coping with things to do) within the past month. Responses are formatted as a 5-point Likert scale ranging from 0 ("Never") to 4 ("Very Often"). Negatively worded items (4, 5, 7, and 8) are reverse scored, and then, all items are summed to generate a total score, with higher scores indicating greater perceived stress.

Social Support

The Medical Outcome Study Social Support Survey [37] is a 19-item self-report survey used to measure perceived social support. The survey asks how often the different kinds of support are available to the respondent as needed, divided into three domains: emotional or informational support, affectionate support, and positive social interaction. Responses are formatted as a 5-point Likert scale ranging from 1 ("None of the Time") to 5 ("All of the Time"). The items are averaged, with higher scores indicating greater availability of social support.

Gratitude

The Gratitude Questionnaire 6-Item version [38] is a self-report survey used to measure a general tendency to experience gratitude (eg, being appreciative of people, events, and situations). Responses are formatted as a 7-point Likert scale ranging from 1 ("Strongly Disagree") to 7 ("Strongly Agree"). Negatively worded items are reverse scored, and then, all items are summed to generate a total score, with higher scores indicating greater gratitude.

Optimism

The Life Orientation Test Revised [39] is an 11-item self-report survey used to measure a tendency toward optimism (ie, expecting the best in uncertainty and expectations on whether good or bad things will happen). Responses are formatted as a 5-point Likert scale ranging from 0 ("Strongly Disagree") to 4 ("Strongly Agree"). Negatively worded items are reverse scored, and then, all items are summed to generate a total score, with higher scores indicating greater optimism.

Coping Ability

The Measure of Current Status Part A [40] is a 13-item self-report survey used to assess perceived ability to cope (eg, capability to use coping techniques, being able to recognize stress). Responses are formatted as a 5-point Likert scale ranging from 0 ("I Cannot Do This At All") to 4 ("I Can Do This Extremely Well"). The measure yields four subscales: relaxation, awareness of tension, assertiveness, and coping confidence. Items pertaining to each subscale are summed, with higher scores on each subscale indicating greater ability to cope in each respective manner.

Mindfulness

The Cognitive and Affective Mindfulness Revised [41] scale is a 12-item self-report survey used to measure mindfulness (ie, the ability to pay attention to the present moment in a nonjudgmental manner). The survey asks the respondent to indicate how often they related to their thoughts and feelings mindfully (eg, focused on the present moment, ability to concentrate). Responses are formatted as a 4-point Likert scale ranging from 1 ("Rarely or Not at All") to 4 ("Almost Always"). Negatively worded items are reverse scored, and then, all items are summed to generate a total score, with higher scores representing greater mindfulness.

Empathy

The 7-item empathic concern subscale of the Interpersonal Reactivity Index [42] is a self-report survey used to measure empathy (ie, feeling concerned for others, being protective of

others, and being sensitive to others). Responses are formatted as a 5-point Likert scale ranging from 1 ("Does Not Describe Me Well") to 5 ("Describes Me Very Well"). Items are summed to generate a total score, with higher scores indicating greater empathy.

Perceived Improvement

The Patient Perception of Improvement (PPI) [43] is a single self-report item that asks the question, "Do you think that you are now better, about the same or worse as compared to before the intervention?" The item was modified for our study to assess perceived improvement in QoL by asking, "Do you think your quality of life is now better, about the same or worse as compared to before the intervention?" Response options are "Substantially worse," "Minimally worse," "About the same," "Minimally better," and "Substantially better." Separate items are used for each QoL domain (physical health, psychological health, social relationships, and environmental health). This assessment is delivered at posttraining and at 6- and 12-month follow-ups.

Data Analysis

Power Analysis

SAS version 9.4 was used to calculate the power analysis. The effective SDs for the change from baseline to posttraining in physical health and psychological health QoL based on a repeated-measures analysis of variance (ANOVA) of our preliminary data [11] were 14.7 and 10.4 units, respectively. The effective SDs from posttraining to 6-month follow-up were 11.4 and 10.0 units, respectively. Based on these estimates, assuming an MCID of 6.25 units, allowing up to 5% loss to follow-up by posttraining assessment, and testing each of the coprimary outcomes at $P<.03$ (two-tailed), a total of 224 participants will afford 80% power for physical health-related QoL and 96% power for psychological health QoL. Allowing up to 20% loss to follow-up by the 6-month assessment, the study will have 99% power to declare noninferiority of 3RP-NF versus HEP-NF if the true treatment-dependent difference in the maintenance of any change from baseline to posttraining is zero.

Primary and Secondary Outcomes

SAS version 9.4 will be used for the statistical analyses. Treatment effects on primary and secondary outcomes will be analyzed using a shared-baseline, linear mixed model with fully unstructured covariance among up to four repeated measures (baseline, posttraining, and 6- and 12-month follow-ups). The mixed model uses all available data. Participants with missed assessments and those lost to follow-up are included in the analysis. The estimated covariance among repeated measures implicitly imputes missing data. Thus, the model yields unbiased estimates if any missing data are predictable from the observed assessments. Compliance with the intervention and attendance during the group sessions specifically will not be included in the analyses of treatment effect. It is impossible to deduce whether any observed association between outcomes and attendance reflects the effects of increased training on the outcomes or effects of differential outcomes on attendance. It is equally plausible that participants experiencing better outcomes are more likely to attend training sessions as attending additional training sessions improves outcomes. The shared-baseline assumption reflects the true state of the population prior to randomization, and it has the benefit of adjusting for chance differences at baseline [44]. For each outcome, we will compare the effect of 3RP-NF versus HEP-NF on changes from baseline to posttraining and to 6- and 12-month follow-up times using linear contrasts and will report point estimates and their 95% CIs. The two coprimary outcomes will be declared significant for $P<.05$ two-tailed. Persistence of a benefit from 3RP-NF from posttraining to 6- and 12-month follow-up times will be analyzed as a noninferiority test of durability. Noninferiority of 3RP-NF in maintaining benefits relative to HEP-NF will be declared if the lower one-sided 95% confidence bound for a given coprimary outcome is less than 6.25 units (the estimated MCID) in favor of HEP-NF. Several sensitivity analyses will be explored using alternative models. Changes in the scores calculated from baseline to posttraining and to 6- and 12-months will be separately analyzed using Wilcoxon rank sum test to avoid any parametric assumptions about the data. More parsimonious covariance structures will be considered using random participant-specific intercepts, slopes, and quadratic terms (ie, growth curve analysis). Baseline parameters such as NRS pain and their interactions with visit will be included to account for chance differences due to randomization and to explain sources of variation in responses that are independent of the treatment group. All randomized participants will be included in our primary efficacy analyses as randomized, following the intention-to-treat principle.

Mediation and Moderation Analyses

If the 3RP-NF intervention improves some or all of the coprimary and secondary outcomes compared with HEP-NF, we will explore the extent to which this relationship is mediated by psychosocial variables (eg, depression, anxiety, pain interference, and pain intensity). The degree to which a given psychosocial variable mediates the effect of 3RP-NF treatment on a given outcome will be estimated from the pure natural indirect effect from a causal model that includes potential interaction between the intervention and the mediator but assumes no unmeasured confounders [45]. Changes in scores from baseline to each follow-up assessment will be analyzed. Evidence of mediation will be inferred if the CI does not cover zero. The mediation effect size will be determined by the proportion of the total effect that is attributable to the mediation (ie, the mediated effect divided by total effect). This method is consistent with that of Baron and Kenny [44] and has been updated by Kraemer et al [46]; however, it extends the analysis by allowing us to test the significance of the mediated effect and quantify the magnitude of the mediation.

The possible effect of moderators of a beneficial effect of 3RP-NF will be investigated by adding a given moderator (eg, contrasting treatment response by NF1, NF2, and Schwannomatosis), moderator × treatment, and moderator × treatment × visit interaction terms to the repeated-measures ANOVA using methodology described for analyses of primary outcomes. The specific linear contrasts of the moderator × treatment × visit interaction terms will be used to test for differential 3RP-NF dependent benefit in improvements from

baseline to posttraining and to 6- or 12-month follow-up that are a function of diagnosis, age, and race or ethnicity. While we have not designed the study to have a good power to detect differences based on NF type, we have optimized our power to detect differences based on NF type by stratifying randomization by diagnosis, given the available sample size and distribution of NF types.

We will develop WHOQOL-BREF MCID thresholds specific for NF using an anchor-based approach based on participants' self-reports of important changes on the PPI. We will use mixed model cumulative logistic regression to model ordinal responses on the PPI. Each model will include fixed effects of physical health QoL or psychological health QoL and follow-up visit and random participant-specific intercepts to account for correlations among repeated measures. If the variable "visit" (ie, baseline, posttraining, and 6- and 12-month follow-ups) is not significant, it will be dropped from the model. The estimated MCIDs will be the ones that best discriminate participants who report being "About the same" versus "Minimally better" on the PPI, that is, the physical health- or psychological health-related QoL score for which the predicted probability of being "About the same" and "Minimally better" on the PPI is equal.

Data Management

To maximize accuracy and security, all survey data are collected and stored on a secure and HIPAA-compliant Web-based REDCap [29] data system hosted by our academic medical center. Data are stored on password-protected computers that are kept at secure locations. Paper data files (with coded subject identification) are stored in a locked filing cabinet accessible only to the research team. A unique anonymous identifier is assigned to each subject; subsequently, all collected data are associated exclusively with this identifier. This includes all questionnaires administered over the course of the study as well as home practice logs.

Results

The trial is ongoing. Thus far, we have recruited 55 patients and aim to recruit a total of 224. Recruitment will close in May 2020; we plan to complete data analyses by June 2021.

Discussion

NF is a prevalent and incurable condition associated with decreased QoL and high psychosocial comorbidities. The current standard of care for NF is predominantly biomedical. Using a sequential approach and direct feedback from patients, we adapted an evidence-based mind-body program (the 3RP) for the specific needs of patients with NF (3RP-NF). In a pilot RCT, we showed that 3RP-NF has excellent feasibility and acceptability [11]. Moreover, we showed that participation in 3RP-NF was associated with sustained improvement in QoL, psychosocial functioning [11], and multiple dimensions of resiliency [13] (eg, perceived coping ability, perceived social support, and mindfulness) relative to an educational program tailored for the needs of patients with NF (HEP-NF). To remove barriers to care for this rare disease and to increase generalizability, both programs were delivered to patients with NF1, NF2, and Schwannomatosis across the United States and internationally using live videoconferencing.

This paper describes the study design and specific strategies used to conduct an innovative, fully powered RCT of 3RP-NF versus HEP-NF administered via live videoconferencing to adult patients with NF across the United States and internationally. We provide details on the benefits and challenges of delivering psychosocial care using secure live videoconferencing, procedures for keeping participants blinded throughout study participation, means of accommodating patients from different time zones, techniques for keeping patients engaged in treatment, and methods of monitoring and addressing the safety of participants. This information is invaluable for future trials using live videoconferencing, and it represents a novel model for delivery of care to patients with rare diseases or to those in remote areas.

Results of this trial will not only provide important information on the efficacy and durability of 3RP-NF versus HEP-NF over a year but also allow us to understand whether the specific targets of the 3RP-NF interventions—mindfulness, coping, social support, optimism, and others—are plausible mechanisms for improvements in the primary outcomes. We will also be able to address whether any benefits of 3RP-NF are dependent on demographic variables, NF type, or self-reported learning disability. Furthermore, using direct feedback from patients, we will be able to calculate NF-specific MCID scores for the physical health- and psychological health-related QoL measures, which will allow a patient-specific evaluation of improvement in the four domains of QoL.

Both the 3RP-NF and the HEP-NF have been adapted iteratively based on feedback from patients with NF and have showed excellent feasibility, acceptability, and preliminary efficacy in our prior work. If the current trial replicates our prior pilot study [11,13] and confirms our hypotheses that 3RP-NF is superior to HEP-NF in improving physical health QoL and psychological health QoL as well as other secondary outcomes, we aim to implement and disseminate 3RP-NF as part of standard of care through the major NF centers within the United States and internationally as well as through CTF. Using the CTF-sponsored annual clinic's meeting and general support from CTF, we would aim to train a variety of providers (eg, psychologists, social workers, nurses, genetic counselors). The original 3RP has been delivered successfully in clinical practice at our institution by nonpsychologists.

Despite the novelty of this trial, there are several limitations. First, although we are using extensive national and international recruitment modalities, recruiting ethnically and racially diverse participants is challenging. Our pilot RCT [11] enrolled primarily white patients, and we have strategies in place to diversify our patient population. Specifically, we have a strong presence in the NF community and have developed a recruitment video that includes racially diverse patients with NF who positively describe their experiences within the study. Second, although we are recruiting international patients, we are delivering the program and assessments in English only. Patients who are not fluent in English are not able to enroll. If the results

of this RCT show that the 3RP-NF is an efficacious program, future work will involve translation of 3RP-NF as part of international dissemination efforts. Furthermore, the majority of patients with NF1 enrolled in both our pilot study and current trial do not have severe cutaneous tumors, suggesting that these patients may not be comfortable participating in a group intervention due to appearance-related concerns. In addition, although we took extensive measures to keep participants blinded to HEP-NF and 3RP-NF, we risk unblinding participants who searched for our research [11,13].

In summary, this is the first psychosocial RCT delivered via live videoconferencing in patients with NF, and it provides valuable information about the design, structure, challenges, and benefits associated with this study design and delivery modality. Results will inform implementation efforts and future clinical trials in other NF populations (eg, adolescents with NF1 and NF2, parents of children with NF1 and NF2, and adults with NF2 who are deaf) as well as other trials targeting geographically diverse individuals with rare diseases. Moreover, our findings will potentially extend the applicability of the 3RP mind-body program core skills to other medical populations and increase our understanding of the mechanisms of its efficacy across medical populations.

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Authors' Contributions

AMV designed the study, wrote the manuscript, and is the principal investigator of the DOD grant; ELZ cowrote manuscript and is the program manager on the DOD grant; CJF cowrote manuscript and is the research assistant on the DOD grant; EAM wrote the analyses plan; JM, ERP, JTJ, and SRP edited the manuscript; and JTJ and SRP referred participants.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report from the Department of Defense office of the Congressionally Directed Medical Research Programs (CDMRP).

[PDF File (Adobe PDF File), 212KB - resprot_v7i10e11008_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
CTF: Children's Tumor Foundation
DOD: Department of Defense
HEP-NF: Health Enhancement Program for Neurofibromatosis
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
MCID: minimal clinically important difference
NATS: negative automatic thoughts
NF: neurofibromatosis
PI: principal investigator
PPI-4: Perceived Stress Scale 4-item
PSS: Patient Perception of Improvement
QoL: quality of life
RCT: randomized controlled trial
RR: relaxation response
SMART: Specific, Measurable, Attainable, Realistic, and Time-based
SMP: Stress Management Programs
WHOQOL-BREF: World Health Organization Quality of Life Brief version

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Protocol

Connectivity as a Predictor of Responsiveness to Transcranial Direct Current Stimulation in People with Stroke: Protocol for a Double-Blind Randomized Controlled Trial

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Abstract

Background: Stroke can have devastating consequences for an individual's quality of life. Interventions capable of enhancing response to therapy would be highly valuable to the field of neurological rehabilitation. One approach is to use noninvasive brain stimulation techniques, such as transcranial direct current stimulation, to induce a neuroplastic response. When delivered in combination with rehabilitation exercises, there is some evidence that transcranial direct current stimulation is beneficial. However, responses to stimulation are highly variable. Therefore biomarkers predictive of response to stimulation would be valuable to help select appropriate people for this potentially beneficial treatment.

Objective: The objective of this study is to investigate connectivity of the stimulation target, the ipsilesional motor cortex, as a biomarker predictive of response to anodal transcranial direct current stimulation in people with stroke.

Methods: This study is a double blind, randomized controlled trial (RCT), with two parallel groups. A total of 68 participants with first ever ischemic stroke with motor impairment will undertake a two week (14 session) treatment for upper limb function (Graded Repetitive Arm Supplementary Program; GRASP). Participants will be randomized 2:1 to active:sham treatment groups. Those in the active treatment group will receive anodal transcranial direct current stimulation to the ipsilesional motor cortex at the start of each GRASP session. Those allocated to the sham treatment group will receive sham transcranial direct current stimulation. Behavioural assessments of upper limb function will be performed at baseline, post treatment, 1 month follow-up and 3 months follow-up. Neurophysiological assessments will include magnetic resonance imaging (MRI), electroencephalography (EEG) and transcranial magnetic stimulation (TMS) and will be performed at baseline, post treatment, 1 month follow-up (EEG and TMS only) and 3 months follow-up (EEG and TMS only).

Results: Participants will be recruited between March 2018 and December 2018, with experimental testing concluding in March 2019.

Conclusions: Identifying a biomarker predictive of response to transcranial direct current stimulation would greatly assist clinical utility of this novel treatment approach.

Trial Registration: Australia New Zealand Clinical Trials Registry ACTRN12618000443291; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618000443291 (Archived by WebCite at http://www.webcitation.org/737QOXXxt)

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KEYWORDS

electroencephalography; magnetic resonance imaging; rehabilitation; stroke; transcranial direct current stimulation; upper limb

Introduction

Globally, stroke is a leading cause of death and disability. According to the World Health Organization, there were 6.7 million stroke-related deaths in 2012, with 33 million stroke survivors living with persistent disability, requiring long-term care and secondary prevention measures [1]. A stroke affecting the sensorimotor network can lead to behavioral impairments, restricting the capacity to perform various activities of daily living. As a result, many stroke survivors require multidisciplinary rehabilitation to help restore function [2]. Despite lengthy periods of rehabilitation, significant impairments often remain, suggesting there is a need to do more to assist survivors of stroke.

Restitution of upper limb function following stroke is important to improve capacity to undertake activities of daily living and enhance quality of life. Underpinning functional restitution is a process known as neuroplasticity where both structure and function of the surviving brain tissue can change to optimize behavior. Research indicates there may be a time-limited window of enhanced neuroplasticity following stroke [3,4]. This period of enhanced neuroplasticity following stroke has many similarities to those that occur during development where the brain is highly plastic and rapid learning occurs [3]. Delivering rehabilitative therapies during this time may provide an opportunity for a more complete recovery. It is generally thought that this period of enhanced neuroplasticity occurs early after stroke [3,4]. In support of this, behavioral evidence indicates that therapy delivered early after stroke may be more effective than that delivered later [3,5,6]. Furthermore, consensus statements suggest that delayed initiation of rehabilitation is associated with poor outcomes and longer hospital stay [7,8]. However, it should be noted that while early therapeutic intervention may be more effective, recovery long after stroke remains possible. In support of this, there is good evidence indicating that constraint induced movement therapy is capable of improving function months or years after the initial stroke [9-11], suggesting the window for recovery may never really close [3].

One interesting approach to stroke rehabilitation is to attempt to reestablish a period of enhanced neuroplasticity to boost the effects of therapy in people with stroke. The potential for a more complete functional recovery by re-establishing a period of enhanced neuroplasticity was recently shown in an animal model of stroke [12]. In this study, Zeiler et al [12] demonstrated that a second ischemic event reopened a period of heightened response to training, facilitating recovery from the initial stroke. While this approach to facilitate functional recovery may not be appropriate in humans, it does suggest that increased responsiveness to therapy can be achieved by reestablishing a period of enhanced neuroplasticity.

Noninvasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), are novel approaches that may be able to facilitate neuroplasticity. It is thought that tDCS is capable of altering the level of intrinsic postsynaptic activity depending on the direction of current flow [13,14]. When applied to the primary motor cortex (M1), anodal tDCS increases cortical network excitability, and cathodal tDCS decreases cortical network excitability. Changes in excitability induced by tDCS are thought to be mediated by long-term potentiation and long-term depression-like synaptic plasticity [13,14]. Several studies have demonstrated functional improvements in people with stroke, following plasticity protocols applied to the lesioned M1 [15,16]. However, recent reviews highlight that, at the group level, tDCS does not provide additional benefits to therapy [17]. Upon further investigation, it appears responses can be highly variable among individuals, suggesting this is not a one-size-fits-all treatment. Several factors are known to influence the response to tDCS, including properties of the stimulated brain network, genetics, and endogenous cortisol levels [18,19]. Recently, we demonstrated that a measure of connectivity of the stimulated network was a strong predictor of response to anodal tDCS in healthy adults [20]. Using electroencephalography (EEG), we found that connectivity between electrodes overlying the stimulated M1 and the ipsilateral parietal cortex in the high beta frequency (20-30 Hz) predicted 69% of variability in the neuroplastic response to anodal tDCS using a leave-one-out and predict analysis. Along similar lines, connectivity of the stimulated ipsilesional motor network in alpha frequency (8-13 Hz) was strongly associated with the change in corticospinal excitability following tDCS in people with stroke [21].

Further evidence of the role that functional brain networks may play in modulating response to tDCS is available from other clinical populations. For example, in people with fibromyalgia, connectivity among the thalamus, posterior insula, motor cortex and sensory cortex was a marker of better analgesic response following tDCS applied to M1 [22]. Similarly, responses to tDCS applied to the dorsolateral prefrontal cortex in people in a minimally conscious state were associated with connectivity between the dorsolateral prefrontal cortex and inferior frontal gyrus [23]. It may be that the connectivity of the network targeted by tDCS can be a useful predictor of responsiveness to brain stimulation therapy. Indeed, this may be even more critical following a stroke, where damage as a result of the lesion can interrupt functional connectivity [24].

The primary objective of this study is to determine whether connectivity of the cortical target for tDCS modulates responses to this intervention in people with stroke. The secondary objectives of this study are to determine whether facilitatory tDCS applied to the ipsilesional hemisphere in combination with an upper limb exercise program provides greater behavioral improvement compared with sham stimulation and to determine whether additional neurophysiological characteristics, such as lesion size, cortical excitability, and white matter integrity, modulate the responsiveness to tDCS. We hypothesize that the response to anodal tDCS will be variable; participants who have greater functional connectivity of the ipsilesional motor network will have stronger responses to the stimulation as shown by a

greater increase in upper limb function following the intervention period. Outcomes from this study will have important implications for the clinical translation of tDCS in stroke rehabilitation. The ability to select people who will respond to this therapy could substantially improve the clinical translation of this treatment approach.

Methods

Study Design

The SPIRIT (Standard Protocol Items: Recommendations for interventional trials) recommendations were referenced when developing this protocol. This protocol has been registered in the Australian and New Zealand Clinical Trials Registry (ACTRN12618000443291). This study is a double blind, randomized controlled trial, with 2 parallel groups. Both outcome assessors and participants will be blind to allocation. Randomization will be performed using a computerized sequence generation by an external researcher. As our primary research aim is to investigate the brain connectivity of participants allocated to the active treatment group, the allocation will be weighted 2:1 toward the active treatment group. A sham treatment group will be used as a comparator to demonstrate the effectiveness of this intervention at the group level and to demonstrate that brain connectivity is not associated with response to sham tDCS.

The study protocol has been approved by the University of South Australia Human Research Ethics Committee (application identification 0000036781; approved May 19, 2017). Recruited participants will provide written informed consent in accordance with the World Medical Association Declaration of Helsinki.

Participants and Recruitment

Stroke participants will be recruited from the community by several strategies including placing information at local acute and tertiary hospitals, advertising through relevant charities and community services (eg, Stroke Foundation Australia and Stroke South Australia), speaking with local stroke survivor support groups, and advertising through social media. Textboxes 1 and 2 present the inclusion and exclusion criteria.

Sample Size

Our primary aim is to determine the characteristics of the sensorimotor network at baseline that may predict the responsiveness to anodal tDCS in people with stroke. Therefore, our sample size calculation was based on pilot data of 10 people with stroke where we observed a medium to large effect size (r=0.56) for a correlation between baseline high beta frequency connectivity and change in cortical excitability following anodal tDCS [21]. Using this effect size with alpha set at .05 and power of 95%, we determined a total sample of 47 would be required. However, we will aim to recruit a total sample of 68, given our methodological approach of using unequal group allocation (additional 12%) and the nature of the home-based treatment with a longer follow-up study period (allowing 30% dropout). This will result in 45 participants in the active treatment group and 23 participants in the control group.

Experimental Protocol

Participants will attend 6 experimental sessions, as outlined in Figure 1. Session 1 will be conducted at the Clinical Research and Imaging Centre (Dr Jones and Partners, South Australian Health and Medical Research Institute) where magnetic resonance imaging (MRI) sequences will be performed to obtain structural, diffusion, and functional images. Session 2 will be conducted within 5 days of the initial MRI scan at the University of South Australia, City East Campus, Clinical Trials Facility. Participants will be encouraged to attend this experimental session with a supportive family member, friend, or carer. In this session participants will undergo baseline neurophysiological and behavioral outcome assessments and will be provided with a home tDCS kit (NeuroConn DC-Stimulator Mobile, NeuroConn GmbH, Ilmenau, Germany). Participants and their support person will be trained in the use of the home tDCS, iPad, and the Graded Repetitive Arm Supplementary Program (GRASP) exercises. In addition, information sheets will be provided for the use of the home tDCS equipment and the iPad. This information will detail the correct use of equipment, including locating the correct spot for tDCS electrode position, which will be marked on the scalp with a permanent marker. To facilitate training, the first of 14 treatments will be undertaken at the Clinical Trials Facility under the supervision of a research staff member. An iPad will be provided to each participant to facilitate monitoring of home tDCS using a telehealth platform. Each iPad will be preloaded with a videoconferencing platform (Skype), allowing the research staff to monitor the tDCS set-up and use across the intervention period.

Experimental sessions 3, 5, and 6 are respectively performed immediately, 1 month and 3 months following the final home tDCS treatment. During these sessions, participants will undergo neurophysiological and behavioral outcome assessments. Experimental session 4 is a follow-up MRI session and will occur within 5 days of the final tDCS treatment.

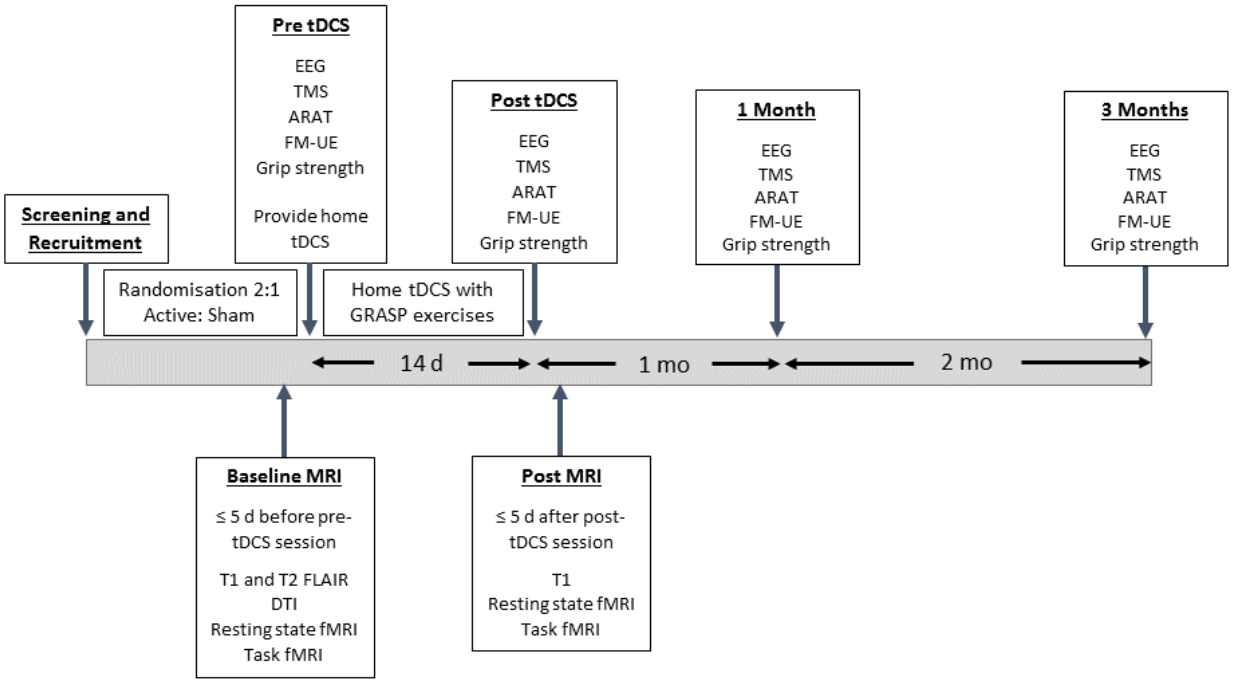
Textbox 1. Inclusion criteria

- Aged ≥18 years of age
- At least 6 months after the first ever stroke with motor impairment
- Measurable impairment of the upper limb (Fugl-Meyer upper extremity of <62 out of 66)
- Supportive family, friends, or carers willing to actively assist and motivate across the 2-week intervention
- Active wrist extension of, at least, 5°
- Active index finger flexion of, at least, 10°
- Modified Ashworth scores of <4 for the affected elbow, wrist, and metacarpal phalangeal joints

Textbox 2. Exclusion criteria

- Transcranial magnetic stimulation and transcranial direct current stimulation safety exclusion criteria as per international guidelines [25]
- Contraindications for magnetic resonance imaging
- Self-reported neglect, apraxia, or shoulder pain (>4 out of 10 on pain visual analog scale) that would affect the ability to undertake a 1-hour upper limb exercise program.
- Language or cognitive impairment that would limit the ability to communicate with the research team by videoconference
- Participation in a concurrent research study or clinical program for upper limb rehabilitation.

Figure 1. The schematic diagram of the experimental sessions. tDCS: transcranial direct current stimulation; EEG: electroencephalography; TMS: transcranial magnetic stimulation; ARAT: action research arm test; FM-UE: Fugl-Meyer Upper Extremity; GRASP: Graded Repetitive Arm Supplementary Program; MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; DTI: diffusion tensor imaging; fMRI: functional magnetic resonance imaging.



Intervention

Graded Repetitive Arm Supplementary Program

All participants will be provided with a home exercise program using the GRASP [26]. The GRASP protocol consists of a booklet with detailed descriptions of multiple exercises for strength, range of motion, fine motor, and goal-directed activities targeting the upper limb. The provided kit includes all required equipment to perform the exercise program. The GRASP protocol is a self-administered program with program levels (grades 1-3) individualized by a qualified occupational therapist, based on the level of impairment of the upper limb. The upper limb exercises will be performed for 1 hour per day over a 2-week period (14 sessions).

Transcranial Direct Current Stimulation

Participants will also be provided with a home tDCS kit, which will be preprogrammed for 14 sessions of active or sham stimulation using a study code to facilitate research staff blinding. Participants will be unable to modify, or observe, any settings of the home tDCS devices. To initiate stimulation, participants will simply position electrodes on the head and press the start button. Those randomized to the “active” arm of the study will receive tDCS while simultaneously performing the GRASP exercises. TDCS will be delivered for 20 minutes and occur at the same time that a participant is undertaking the 1-hour GRASP program. Therefore, the initial 20 minutes of the intervention will involve both tDCS and the GRASP, with the remaining 40 minutes involving only GRASP exercises. The electrodes will be positioned with the anode over the ipsilesional M1 and cathode over the contralateral supraorbital region. TDCS will be applied at an intensity of 1 mA for 20 minutes daily for 2 weeks (total of 14 sessions) at home. Stimulation will be ramped up from 0 mA to 1 mA over the first 30 seconds and down from 1 mA to 0 mA over the final 30 seconds.

Participants randomized to the “sham” arm of the study will receive sham tDCS while undertaking the 1-hour individualized GRASP exercises. Electrodes will be positioned in the same location as the active tDCS group. Sham tDCS mimics the

sensation of stimulation without changing cortical excitability. The protocol for sham tDCS will ramp the current up from 0 mA to 1 mA over the first 30 seconds before ceasing for the following 19 minutes and 30 seconds. This approach has been shown to provide an effective sham stimulation [27].

Compliance Monitoring

Several strategies will be used to monitor protocol compliance and ensure the correct use of home tDCS (for a summary see Textbox 3). The number of completed tDCS sessions and daily duration of GRASP will be recorded in a treatment diary.

Adverse Events and Assessment of Blinding

At the completion of the 2-week tDCS intervention, participants will be asked to complete a questionnaire to identify any adverse events and establish whether participant blinding was successful. In accordance with current recommendations [28], we will ask participants to rate on a scale of 1-4 (1, absent; 2, mild; 3, moderate; 4, severe) the presence of the following symptoms: headache, neck pain, scalp pain, tingling, itching, burning sensations, skin redness, sleepiness, trouble concentrating, acute mood change, and other symptoms. In addition, we will ask participants to what extent they believe the reported symptoms were related to using tDCS (1, none; 2, remote; 3, possible; 4, probable; 5, definite). Furthermore, we will ask participants to indicate whether they believe they received active stimulation (yes or no) to determine the effectiveness of blinding.

Outcome Measures

Textboxes 4 and 5 summarize the independent and dependent variables to address the primary research question for this study. Participant demographics and clinical characteristics including age, gender, handedness [29], and time since stroke will be recorded and compared between the active and sham groups.

Assessments of Upper Limb Function

The primary outcome measure for this study is a change in upper limb impairment as measured with the Fugl-Meyer upper extremity (FM-UE) assessment. The FM-UE is a commonly used, validated, and reliable measure of sensorimotor impairment [30]. The FM-UE is considered as one of the most comprehensive quantitative measures of motor impairment following stroke.

In addition, upper limb function will be assessed with the action research arm test (ARAT) and grip strength. The ARAT is a valid and reliable measure of hemiplegic upper limb function [31]; it provides a quantitative measure of upper limb function for domains of grip, grasp, pinch, and gross arm movement. Grip strength is associated with motor cortical output and motor recovery [32]. We will measure grip strength using a hand dynamometer (SH5001 Saehan Hydraulic Hand Dynamometer, Saehan Co, Masan, Korea). The best (maximal) grip of 3 attempts will be recorded.

Textbox 3. Strategies to facilitate protocol compliance.

- *Support person*: A support person will attend training for home transcranial direct current stimulation (tDCS) and graded repetitive arm supplementary program (GRASP) exercises to assist, and motivate, participants as required across the intervention.
- *Initial treatment under supervision*: The first treatment will be completed under supervision to ensure the correct use of tDCS.
- *TDCS electrode position marked on scalp*: The correct positioning of tDCS electrodes will be marked on the scalp with a permanent marker to facilitate home application.
- *Information sheet*: Step-by-step instructions for the use of the home stimulator.
- *Videoconference*: In real time, confirm correct tDCS usage, provide motivation, and progress individual exercise programs or GRASP grade. Videoconferences will occur every second day at a minimum and more frequently if required.
- *Exercise diary*: Record daily completion of tDCS and GRASP. Includes recording duration of GRASP therapy, motivation, fatigue, and perceived exercise difficulty.

Textbox 4. Dependent variables

- *Primary*
  - Change in upper limb impairment (Fugl-Meyer Upper Extremity)
- *Secondary*
  - Change in the upper limb function (action research arm test)
  - Change in the upper limb strength (grip strength)
  - Change in the corticospinal excitability obtained from motor-evoked potential amplitude

Textbox 5. Independent variables

- *Functional connectivity*
  - Task functional magnetic resonance imaging
  - Resting state functional magnetic resonance imaging
  - Electroencephalography
- *Structural connectivity*
  - Fractional anisotropy index of the corticospinal tract obtained from diffusion tensor imaging
- *Anatomical*
  - Lesion volume
- *Demographics and clinical characteristics*
  - Age
  - Gender
  - Time since stroke
  - Affected hemisphere based on hand dominance

Outcome assessors will be blind to group allocation and have completed training for FM-UE and ARAT assessments through the University of California Irvine. Training outcome assessors with this approach has been shown to improve accuracy and reduce variance of the FM-UE and ARAT [33,34].

Neurophysiological Testing

Electroencephalography

Functional connectivity between brain regions will be assessed with high-density EEG. Three minutes of EEG will be acquired using an ASA-lab EEG system (ANT Neuro, Enschede, the Netherlands). Participants will be fitted with an ANT Waveguard cap with 64 sintered Ag-AgCl monopolar electrodes in standard 10-10 positions. Signals will be sampled at 2048 Hz, amplified 20X, filtered (high pass, DC; low pass, 553 Hz) and online referenced to CPz. During data recording, participants will be seated in a comfortable chair in a quiet room. Standardized instructions will be delivered to each participant asking them to relax during the 3 minutes of data recording, keep their eyes open, refrain from speaking or moving, maintain their gaze toward a fixation point straight ahead at eye level and not actively engage in any cognitive or mental tasks. Impedance will be kept <5 kΩ while recording.

Artifact rejection will be performed prior to analysis using independent component analysis. Nonphysiological artifacts will be identified using an automated and objective method to remove assessor bias [35]. Preprocessed data of participants with a right hemisphere lesion will then be flipped about the midline so that all lesions appear in the left hemisphere. Functional connectivity between electrodes will be determined using the debiased weighted phase lag index, which is a conservative estimate of connectivity based on phase consistency and biasing against zero phase lag relationships, limiting the detection of spurious measures of connectivity [36]. Regions of interest will include a seed approximating the ipsilesional M1 (C3) and clusters of electrodes approximating the ipsilesional premotor (F5, F3, FC5, and FC3), ipsilesional parietal (CP3, CP5, P3, and P5), and contralesional M1 (C4). Frequency bands of interest are the alpha band (8-15 Hz) and beta band (16-31 Hz) as they are associated with sensorimotor function [20,37,38]. For a given frequency, a debiased weighted phase lag index value of 1 indicates maximal phase coupling, whereas a value of 0 indicates no phase coupling. Connectivity analyses will be performed in MATLAB 9.2.0 (MathWorks, Inc) using both EEGLAB [39] and FieldTrip toolboxes [40].

Transcranial Magnetic Stimulation

Single-pulse transcranial magnetic stimulation will be used to quantify corticomotor excitability of the ipsilesional M1. Monophasic (posterior to anterior current flow) transcranial magnetic stimulation pulses will be delivered with a Magstim 200 stimulator (Magstim, Whitland, United Kingdom) via a figure-of-eight coil (70-mm wing diameter). The coil will be placed tangentially over the scalp with the handle pointing 45° posterolateral. Surface electromyography will be used to record motor-evoked potentials (MEPs) from the first dorsal interosseous muscle of the paretic hand with electrodes positioned in a belly-tendon montage. Suprathreshold stimuli will be delivered over the ipsilesional hemisphere to identify the optimal position for evoking an MEP from the first dorsal interosseous muscle of the paretic hand. For participants where MEPs cannot be evoked even at maximal stimulator output as a result of the stroke, we will document that a measure of corticospinal excitability was not obtainable at that experimental session. For participants where MEPs can be evoked, the optimal site will be marked on the scalp using a felt-tip marker to ensure consistent coil placement during subsequent data collection. Resting motor threshold will then be determined and is defined as the minimum stimulus intensity required to evoke an MEP of at least 50 μV in at least 5 of 10 consecutive trials. Thirty stimuli, not contaminated by pre-stimulus electromyography, will then be obtained at 120% resting motor threshold (interstimulus interval 4.5-5.5 sec) with the average,

peak-to-peak amplitude, determined as a reliable measure of corticospinal excitability [41].

Magnetic Resonance Imaging

MRI will be performed at the Clinical Research and Imaging Centre located at the South Australian Health and Medical Research Institute with a Siemens 3T MAGNETOM Skyra scanner (Siemens, Erlangen, Germany). Standard MRI safety screening will be performed to ensure included participants are safe for MRI. At the preintervention MRI session, the imaging protocol will have a duration of 45 minutes and include T1 MPRAGE and T2-weighted fluid-attenuated inversion recovery images, diffusion tensor imaging, resting state, and task functional MRI (fMRI). At the postintervention MRI session, the imaging protocol will have a duration of 30 minutes and include T1-weighted images, resting state fMRI, and task fMRI.

The imaging protocols are as follows: T1-weighted images (MPRAGE, voxel 1 mm × 1 mm × 1 mm, repetition time (TR)=2300 ms, echo time (TE)=2.98 ms, flip angle=9°), T2-weighted fluid-attenuated inversion recovery images (voxel 1 mm × 1 mm × 1 mm, TR=5000 ms, TE=393 ms), diffusion MRI (voxel 2 mm × 2 mm × 2 mm, TR=4200 ms, b-value=0 and 2000 s mm), resting state fMRI (voxel 2.4 mm × 2.4 mm × 2.4 mm, TR=735 ms, TE=36 ms, 2 repeats of 6-min duration, 490 measurements for each), and task fMRI (voxel 2 mm × 2 mm × 2.5 mm, TR=3000 ms, TE=30 ms, 4.44-min duration). During the task fMRI, participants will be presented with a visual cue to squeeze a stress ball in their paretic or nonparetic hand, with blocks alternating every 30 seconds and repeated 4 times per hand.

Preprocessing and statistical analyses of MRI data will be carried out using tools from the FMRIB Software Library [42]. For all voxel-wise analyses, images from participants with lesions of the right hemisphere will be flipped about the midline after registration to standard space so that all lesions appear in the left hemisphere. fMRI data will be preprocessed and analyzed using the FMRIB Expert Analysis Tool [43]. Preprocessing steps will include high-pass temporal filtering at 0.01 Hz, spatial smoothing, motion correction, and removal of nonbrain tissue. Task fMRI data will be analyzed with a boxcar regressor, which will model task and rest blocks for first-level statistical maps for each participant. Higher level mixed-effects analysis will then be run using FMRIB Local Analysis of Mixed Effects [43] to test correlations with improvement in clinical scores and compare activation maps across groups.

For resting state fMRI, nuisance regressors of no-interest (cerebrospinal fluid, white matter, head motion, and physiological noise) will be modeled and removed. We will then calculate the mean time course of the blood-oxygenation level dependent signal in all voxels of the ipsilesional M1 region of interest. This time series will then be entered separately as an explanatory variable in the general linear model to determine for each participant the voxels where blood-oxygenation level dependent signal is temporally correlated with the ipsilesional M1. Connectivity between the ipsilesional M1 and other regions of interest (contralesional M1, ipsilesional dorsal premotor cortex, ipsilesional ventral premotor cortex, ipsilesional supplementary motor area, and ipsilesional posterior parietal cortex) will be determined with a Pearson's correlation coefficient. Connectivity of the ipsilesional M1 will be compared before and after tDCS with a general linear model.

Structural connectivity will be analyzed with the FMRIB Diffusion Toolbox [44]. For each participant, the mean fractional anisotropy (FA) of the posterior limb of the internal capsule will be determined. An asymmetry index will be calculated as follows: FA = (FA–FA) / (FA+FA).

Lesion volume will be defined by manually tracing the lesion in FLS view. Lesions will be traced from each participant's T1-weighted image using the coregistered T2-weighted image as a reference for lesion extension.

Statistical Analysis

Normality of data will be confirmed using Shapiro-Wilk normality tests. Where required, data will be normalized using transformations or nonparametric statistics applied. Participants' demographics and clinical characteristics will be compared between active and sham groups. The effect of the intervention on behavioral and neurophysiological outcome measures will be investigated with a 2 Group (active, sham) × 4 Time Point (Baseline, Postintervention, 1-Month Follow-up, 3-Month Follow-up) repeated measures analysis of variance. Independent variables (Textbox 5) will be correlated with the primary outcome measure for response to anodal tDCS (change in upper limb impairment measured with the UE-FM). Where appropriate, regression models will be generated using those independent variables significantly correlated with change in upper limb impairment to identify a combination of measures associated with response to anodal tDCS. Any regression models generated will be compared using the Bayesian information criteria [45]. Where appropriate, the predictive capacity of the generated model will be investigated using a leave-one-out cross-validation. This cross-validation will be performed on participants allocated to both active and sham treatment groups to demonstrate that the predictive model is specific to the stimulation group. Statistical testing will be performed using SPSS (IBM Co, version 24.0) and significance level will be $P \leq .05$.

Results

As of April 2018, 11 participants have been enrolled in the study with 5 beginning experimental testing. It is anticipated that the final participant enrollment will occur in December 2018, with data collection completed in March 2019. At the conclusion of the study, results will be disseminated through publication in scientific journals and conference presentations.

Discussion

Adjuvant therapies, such as tDCS, are critical to improving the potential for motor function recovery following stroke. To date, the response to tDCS has proved highly variable, and this has limited clinical translation. This is likely due, at least in part, to stimulation being applied without consideration of individual motor network characteristics. This study will be a significant step forward in the development of precision approaches for the use of brain stimulation in stroke rehabilitation. This will

be achieved by providing evidence for biomarkers of brain connectivity to selectively apply tDCS to those stroke patients who will benefit most. Future work could lead to individualized brain stimulation protocols based on motor network connectivity and clinical presentation. This body of work has the potential to enhance functional outcomes for a population that presents a significant social and economic burden and are desperate for improved rehabilitation services.

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Authors' Contributions

EW led the writing of this manuscript. BH conceived the study design and was successful in obtaining funding to support this research. MR and SH contributed to the study design and reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report from the Sylvia and Charles Viertel Charitable Foundation.

[PDF File (Adobe PDF File), 185KB - resprot_v7i10e10848_app1.pdf]

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Abbreviations

ARAT: action research arm test
EEG: electroencephalography
FA: fractional anisotropy
fMRI: functional magnetic resonance imaging
FM-UE: Fugl-Meyer upper extremity
GRASP: graded repetitive arm supplementary program
M1: primary motor cortex
MEP: motor-evoked potential
MRI: magnetic resonance imaging
tDCS: transcranial direct current stimulation

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Protocol

Perioperative Optimization With Nutritional Supplements in Patients Undergoing Gastrointestinal Surgery for Cancer (PROGRESS): Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Postoperative morbidity following gastrointestinal tract major surgery ranges between 40% and 60%. Malnutrition, poor protein intake, and surgery-related impairment of the immune system and its function have been associated with postoperative infections. Supplemental perioperative nutrition may improve nutrition by increasing protein intake to influence cell-mediated immunity, thereby reducing the rate of postoperative infectious complications.

Objective: The primary objective of our trial is to determine the proportion of eligible patients randomized in an 18-month period. The primary feasibility outcome will be to (1) stop, main study not feasible: estimated proportion of randomized patients <40.0% (40/100); (2) continue with protocol modifications: estimated proportion of randomized patients 40.0% (40/100) to 59.0% (50/100); or (3) continue without modification: estimated proportion of randomized patients ≥60.0% (60/100). The secondary objectives are to evaluate compliance with the nutritional supplements and to estimate differences in postoperative complications, global health-related quality of life (QoL), and median length of hospital stay between the groups.

Methods: This is a double-blind randomized placebo-controlled feasibility trial. The intervention comprises three nutritional supplements: a protein isolate powder (ISOlution); immunomodulation (INergy-FLD), formulated liquid diet; and carbohydrate loading (PreCovery). Patients will consume 1 serving of the protein supplement per day from the randomization time up to 6 days before surgery (30 days in total). The immunomodulation, a solution that contains arginine, protein isolate, omega-6 fatty acids, and RNA, aims to attenuate excessive inflammatory responses and to replenish nutrients. This solution will be consumed as 3 doses per day for 5 days before and after surgery. Carbohydrate loading helps to reduce the stress from surgery by decreasing insulin resistance. Patients will have 2 servings the evening before surgery and 1 serving 2-3 hours before surgery. To be eligible, patients must have a resectable gastrointestinal cancer for which an elective operation is planned. Patients will be stratified according to nutritional status. The operation should occur within 4 weeks from enrollment.

Results: We expect to screen 165 eligible patients; 60.6% (100/165) of them will be randomized to either intervention or placebo. Assuming a two-sided alpha of .05, this will give us a 95% CI around the estimate of 53%-68%. A sample size of 50 per group will enable us to estimate the treatment effect and corresponding variance of the complication rate and QoL measures with adequate precision. The success is defined as the proportion of eligible patients randomized as ≥60.0% (60/100). Patients' compliance is defined as an intake of at least 70% (41/58) sachets of the intervention volume.

Conclusions: The results will help to determine the feasibility of a larger randomized controlled trial to implement a perioperative nutritional supplement program for patients undergoing gastrointestinal surgery for cancer.

Trial Registration: ClinicalTrials.gov NCT03445260; https://clinicaltrials.gov/ct2/show/NCT03445260 (Archived by WebCite at http://www.webcitation.org/72CAmMzgP)

International Registered Report Identifier (IRRID): PRR1-10.2196/10491

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KEYWORDS

perioperative care; nutritional supplements; gastrointestinal cancer; gastrointestinal surgery; postoperative outcomes

Introduction

Despite recent advances in surgical techniques and perioperative management, postoperative morbidity, including infectious complications, following major surgery of the gastrointestinal tract remains high, ranging between 40% and 60% [1,2]. Preoperative fasting induces the body to utilize stored nutrients, thereby accelerating the release of stress hormones, exacerbating insulin resistance, delaying wound healing, increasing morbidity and mortality, and extending the length of hospital stay [3]. Additionally, surgery-related impairment of the immune system and its function have been associated with postoperative infections [4,5].

Often, patients undergoing surgery experience disorders of the immune response, which are facilitated by low caloric intake and intestinal bacteria translocation [2]. With surgical trauma, the balance between lymphocyte T helper type 1 (Th1) cells and T helper type 2 (Th2) cells is shifted more toward Th2 cells. Th1 cells secrete interferon-gamma and interleukin (IL)-2, and they induce cell-mediated immune responses, whereas Th2 cells produce IL-4, IL-10, and IL-13, providing help for humoral immune responses [1,6]. Th1 cells activate macrophages and are highly effective in clearing intracellular pathogens, whereas Th2 cells suppress cell-mediated immunity [1]. It is thought that this reported suppression of Th1 response and intensification of Th2 response, often reported in surgical patients, may be one of the factors increasing the susceptibility to infections and septic complications. The presence of any complication within the first 30 days postoperatively is the most important independent determinant of 30-day mortality and overall long-term survival [7]. It has been shown that supplemental perioperative nutrition can influence cell-mediated immunity, the Th1:Th2 differentiation ratio and can help reduce the rate of infectious complications after surgery, thereby improving the rate of long-term survival [1].

Oral supplements or immunonutrition that are considered to boost the immune system in this protocol are defined as a solution that contains nutrients such as arginine and omega fatty acids. Arginine deficiency after surgical stress was first reported over 30 years ago, and recent studies have demonstrated that the perioperative use of an arginine-supplemented diet has the ability to decrease the rate of postoperative infections [8]. Arginine is an amino acid involved in tissue repair and wound healing. It is an essential metabolic substrate for immune cells and required for normal lymphocyte function [9]. In addition, omega fatty acids, such as n-6 and n-3, are derived from fish oil, and they have been shown to attenuate the production of inflammatory compounds and ultimately reduce the cytotoxicity of inflammatory cells [10]. In a phase II trial, docosahexaenoic acid (DHA) supplementation was shown to increase the time to disease progression and overall survival in patients receiving adjuvant chemotherapy for metastatic breast cancer. The median time to disease progression was 3.5 months in the low DHA group and 8.7 months in the high DHA group (P=.02). The median overall survival was 18 months in the low DHA group and 34 months in the high DHA group (P=.007) [11]. Each element works toward improving the immune response against cancer through modulation of excessive inflammatory responses and replenishing depleted nutrients when the body is in a state of stress, such as surgery [11-14].

Along with impaired immune function, surgery increases the release of stress hormones, pushing the body into a catabolic state. These hormones induce the hepatic production of glucose by gluconeogenesis and glycogenolysis and reduce glucose uptake in peripheral tissues, thus leading to postoperative hyperglycemia and a state of and insulin resistance [3]. This period of resistance can be sustained for 3-4 weeks after surgery and is associated with delayed wound healing, increased morbidity, mortality, and prolonged hospital stay. The degree of postoperative insulin resistance is significantly affected by the metabolic status of the patient at the time of surgical stress. The common practice of fasting patients from the evening before surgery is used to avoid pulmonary aspiration after elective surgery. However, there is no evidence to support this [15]. In fact, preoperative fasting increases metabolic stress, hyperglycemia, and insulin resistance [16]. The preoperative protocol has since been updated to allow patients to consume clear fluids until 2 hours before surgery. Preoperative carbohydrate-rich drinks have the ability to achieve a rise in insulin to levels known to change metabolism from a fasted to fed state and reduce postoperative insulin resistance by up to 50% as well as reduce protein loss and improve muscle function [17]. In order to sustain this anabolic state and reduce the degree

of postoperative resistance, it is recommended to consume 100 g of complex carbohydrates the evening before surgery and 50 g up to 2 hours before surgery; this practice has been endorsed by several anesthesiology societies [18].

For patients with gastrointestinal cancer, insufficient protein intake, insulin resistance, and postoperative immobility increase the risk of impaired immune function [19]. Insufficient protein intake also results in slower recovery, prolonging hospital stay and immobility [19]. Nutritional depletion is a major determinant of the development of postoperative complications. It is associated with changes in body composition, tissue wasting, and impaired organ function, which lead to impaired immune and muscle function. Thus, nutritionally depleted patients are at higher risk of infectious complications, and a direct relationship with increased operative mortality independent of the type of surgery has been observed [20]. Patients with gastrointestinal cancers typically experience malnutrition, significant weight loss, and reduced food intake. Thus, optimizing nutritional status both before and after surgery by meeting protein requirements creates an opportunity to reduce patients' postoperative complications [21]. Whey protein substrates have great potential to be used effectively to support postsurgery anabolism. Whey proteins of high quality have proved to be effective in modulating muscle protein synthesis and are a convenient way to supplement protein needs in malnourished patients [22]. Whey proteins also have immunomodulating properties, including biosynthesis of the antioxidant glutathione, which could attenuate the catabolic effects of surgery and spare protein [23]. Albumin, muscle function tests, immunological status, and weight loss have been used to show the correlation between nutrition depletion and postoperative morbidity and mortality.

It has been proposed that perioperative immunomodulation, carbohydrate loading, and increased protein intake may have the potential to decrease overall complications, improve patients' quality of life (QoL), improve disease-free and overall survival, and reduce overall health care cost by decreasing the length of hospital stay and readmissions [24,25].

There is some evidence that each intervention works separately through different mechanisms of action. Therefore, we believe that a combination of the 3 interventions could have an additive effect. We propose to carry out a study to establish the feasibility of a randomized controlled trial comparing perioperative nutritional supplements with placebo, targeted at reducing the postoperative complication rate in patients undergoing gastrointestinal surgery for cancer (NCT03445260). The secondary objectives are to evaluate compliance with the intervention (nutritional supplements) and to estimate differences in postoperative complications and the comprehensive complication index (CCI), which is a scoring system to measure postoperative complications for each patient [26]. The results of this study will provide us with the necessary information to plan a larger multicenter randomized controlled trial. Set criteria for success will be clearly outlined in this proposal to determine whether it is feasible to move forward with a larger trial. The phase III randomized trial would compare the proportion of postoperative complications, patients' QoL, time to initiation of adjuvant chemotherapy, and its effect on disease-free and overall survival as well as costs to the health care system between groups.

This study will focus on supplementing patients' perioperative care with 3 different products administered around the time of surgery: ISOlution, INergy-FLD, and PreCovery. ISOlution is a neutral-tasting protein isolate supplement that contains no fillers, sweeteners, or artificial flavors. It comprises a mixture of whey protein isolate and lecithin and is added to foods and drinks without altering their texture or taste due to its neutral consistency. ISOlution has 93% protein purity, a digestible indispensable amino acid score of 1.09, and 14.3 g of leucine per 100 g of protein, which is an amino acid that has been shown to have an important role in enhancing the anabolic effects of protein. ISOlution can also be administered as a tube feed. INergy-FLD is an immune-modulating solution that contains whey protein isolate, refined fish oil with omega-6 fatty acids, and antioxidants such as vitamins A, C, D, and E and has an elevated amino acid concentration with 4.2 g of L-arginine per serving. It has a natural citrus flavor, low sugar content, and a trace of lactose. Therefore, it can be tolerated by patients who are lactose intolerant. PreCovery contains 50 g of complex carbohydrates per serving, with a 12.5% carbohydrate concentration and easily mixes with water. It has no added sugar, a natural citrus flavor, and maintains a low osmolality of 114 mOsmol/kgH_2 O, which promotes digestion, gastric emptying, and water absorption. These products are to be used as supplements and not as a sole source of nutrition.

The general objective of this study is to improve the postoperative outcomes in patients undergoing any type of gastrointestinal cancer surgery. The primary study objective is to determine the proportion of eligible patients randomized in an 18-month period. The secondary objectives are (1) to determine the proportion of enrolled patients who complete the perioperative nutritional support program (see Secondary Outcomes); (2) to estimate the difference in the proportion of patients experiencing postoperative complications between the intervention and placebo groups at 90 days following the index surgery; (3) to estimate the difference in the CCI (a scoring system to measure postoperative complications) between the 2 groups at 90 days following index surgery; (4) to estimate the difference in the global health-related QoL between groups at 90 days following index surgery; and (5) to estimate the median length of hospital stay for each group.

Methods

Recruitment

This is a single-center placebo-controlled randomized feasibility study comparing the intervention of perioperative nutritional supplements (immunomodulation, carbohydrate loading, and protein isolate) with an identical placebo for each solution in patients with gastrointestinal cancer undergoing surgery. Study participants will be recruited from the Juravinski Hospital and Cancer Centre (JHCC), Ontario, Canada. Participants aged ≥18 years with a resectable type of gastrointestinal cancer (eg, gallbladder, liver, pancreas, stomach, small intestine, colon, or rectum cancer) for which an elective operation is planned (resection vs palliative procedure) will be eligible. Patients with

distant metastasis and patients who are lactose intolerant are also eligible because the amount of lactose in ISOlution and PreCovery is minimal.

Patients will be excluded from the study if they have type 1 diabetes, malabsorption syndrome (eg, chronic pancreatitis), organ failure (liver or kidney), galactosemia, end-stage liver disease with a Child-Pugh score of ≥B [27], end-stage renal disease (stages 3 and 4 with a glomerular filtration rate of 30-59 mL/min per 1.73 m^2 for stage 3 and 15-29 mL/min per 1.73 m^2 for stage 4 [28]), inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and ulcerative colitis, galactosemia, ongoing infection, or poorly controlled type 2 diabetes mellitus (ie, patients who have high blood glucose of 12.0-14.9 mmol/L or higher on a regular basis). Patients who cannot tolerate oral intake (eg, gastric outlet obstruction or delayed gastric emptying), patients currently on steroids, and female patients who are pregnant or lactating will not be included in this study.

In summary, our standard surgical techniques include the following for each specific procedure:

1. Liver resection: ~60% (~50/80) are performed laparoscopically.
2. Pancreaticoduodenectomy: all are performed open; there is no routine placement of feeding jejunostomy; ~70% (~50/70) are performed with the classic approach, while the rest are performed preserving the pylorus.
3. Distal pancreatectomies: ~80% (~16/20) are performed laparoscopically, either spleen-preserving or not, depending on tumor location.
4. Rectal resection: routine total mesorectal excision, ~30% (~10/30) are performed laparoscopically.
5. Colon resections: high ligation of the colic vessels, ~40% (~30/70) are laparoscopic.
6. Gastrectomy: all are performed open with a modified D2 lymphadenectomy (no splenectomy).

Randomization

Randomization will be conducted centrally by the Ontario Clinical Oncology Group (OCOG). Study participants will be identified by screening all patients scheduled for surgery at JHCC. Eligibility must be confirmed by the treating physician or designated prior to enrollment. After confirmation and documentation of written informed consent, patients will be randomized by accessing OCOG's Web-based Interactive Registration and Randomization System. Randomization will be performed according to a prescribed computer-generated schedule.

Stratification

Stratification will be employed prior to enrollment to ensure a balance between treatment arms for a factor that may influence the primary outcome, including the nutritional status of the patient. Prior to randomization, patients' overall risk of malnutrition will be determined using the Malnutrition Universal Screening Tool (MUST) [29]. Patients will be stratified by risk status as low risk of malnutrition (MUST score of 0) versus medium and high risk of malnutrition (MUST score of 1 or 2).

Blinding

This is a double-blinded study design. All research personnel and study participants will be blinded throughout the trial. To ensure all investigators and research personnel remain blinded, the company producing the nutritional supplements and placebo will be responsible for providing the Pharmacy Research Support Services (PReSS) and information technology (IT) technician with the allocation information specific to each lot number. All prepackaged kits for preoperative intake and postoperative intake will be sent directly to PReSS. The kits received by PReSS will include a lot number that will correspond to either the intervention or placebo; however, as mentioned above, the only personnel aware of the lot numbers and associated randomization allocation will be the independent pharmacy lead, pharmacy technicians at PReSS, and the independent IT technician responsible for the randomization sequence. To ensure all research personnel remain blinded to the patients' allocation, PReSS will remove the lot number from each kit. PReSS will also be responsible for the accountability of the supplements throughout the study.

After entering the patient information into the Interactive Registration and Randomization System, PReSS will be responsible for dispensing the appropriate kit number and ensuring the lot number has been blinded from the patient and the research personnel. The individual packets within the kits will be labeled from "30 days before surgery" to "5 days after surgery."

Study Agents

Nutritional Supplements and Placebo

Patients undergoing gastrointestinal cancer surgery will either receive perioperative nutritional supplements or placebo (Multimedia Appendix 1). The operation should occur within 4 weeks from study enrollment. Upon assessment, patients will have a consultation with their physician where standard recommendations on nutrition prior to their surgery will be provided. This consultation will happen in the B3 wing or the Surgical Oncology Clinics of JHCC. Immediately following randomization (same day), patients will receive the intervention or placebo. The intervention consists of the following 3 different solutions.

Protein Isolate Powder (ISOlution)

This will be consumed by the patient to increase muscle protein synthesis and achieve the recommended per meal protein intake prior to surgery as well as after surgery. Each serving delivers 20 g of protein stirred into a minimum of 250 mL of liquid or soft foods. Patients will be asked to consume 1 serving per day (20 g of protein powder in total per day) from the time of randomization up to 6 days before surgery (up to 30 days in total).

Immunomodulation-Formulated Liquid Diet (INergy-FLD)

In preparation for surgery, patients will consume an immune-modulating formula containing various ingredients, including arginine, protein isolate, omega-6 fatty acids, and RNA, aimed to attenuate excessive inflammatory responses

without being immunosuppressive and to replenish nutrients that are depleted in a state of stress (ie, surgery), thereby enhancing the recovery process [1]. The volume of this solution is 250 mL per dose (51 g of powder reconstituted in 250 mL of cold water). Patients will be asked to consume 3 doses per day for 5 days prior to surgery and 5 days following surgery.

Carbohydrate Loading (PreCovery)

On the day of surgery, a carbohydrate-rich solution will be consumed by the patient to reduce the stress of surgery, reduce insulin resistance, and accelerate recovery. The volume of this solution is 400 mL per dose (55 g of powder reconstituted in 400 mL of cold water). It contains 50 g of complex carbohydrates at a 12.5% carbohydrate concentration, including 2 g of glucides or sugars. Patients will be administered 2 servings the evening before surgery and 1 serving 2-3 hours before anesthesia.

Feeding Tube Administration

The intervention or placebo could be administered orally or via alternate enteral feed such as gastrostomy or jejunostomy feeding tubes. ISOlution and INergy-FLD can be administered enterally via oral intake or a tube feed. This procedure is only administered if oral intake cannot be tolerated. For tube feeding administration of ISOlution, mix 1-3 servings into 60-1120 mL of water and stir until completely dissolved; infuse via syringe down the feeding tube; and flush the tube with 30-60 mL of water before and after administration. To administer INergy-FLD via tube feed, mix 1 serving of INergy-FLD with 250 mL of water and stir until completely dissolved and infuse via syringe down the feeding tube; flush the tube as necessary (30-60 mL water). ISOlution and INergy-FLD contain lactose at 0.03 and 0.06 g per serving, respectively. A single threshold of lactose for lactose intolerant subjects cannot be determined. However, the trace amount of lactose found in ISOlution and INergy-FLD is not predicted to cause adverse effects.

Placebo

There will be a placebo control for each of the solutions administered to patients in the intervention arm. The placebo will look exactly as the intervention externally (package) and internally (white powder). Each placebo is composed of a collagen-based filler with exactly the same taste and texture as the intervention. The placebo will be produced and provided by the start-up company Enhanced Medical Nutrition.

Administration

Following randomization, patients will receive blinded packages of either the intervention or the placebo, which will be administered by the PReSS, located in the A4 wing at JHCC. The patients will be responsible for administering their own supplements while at home.

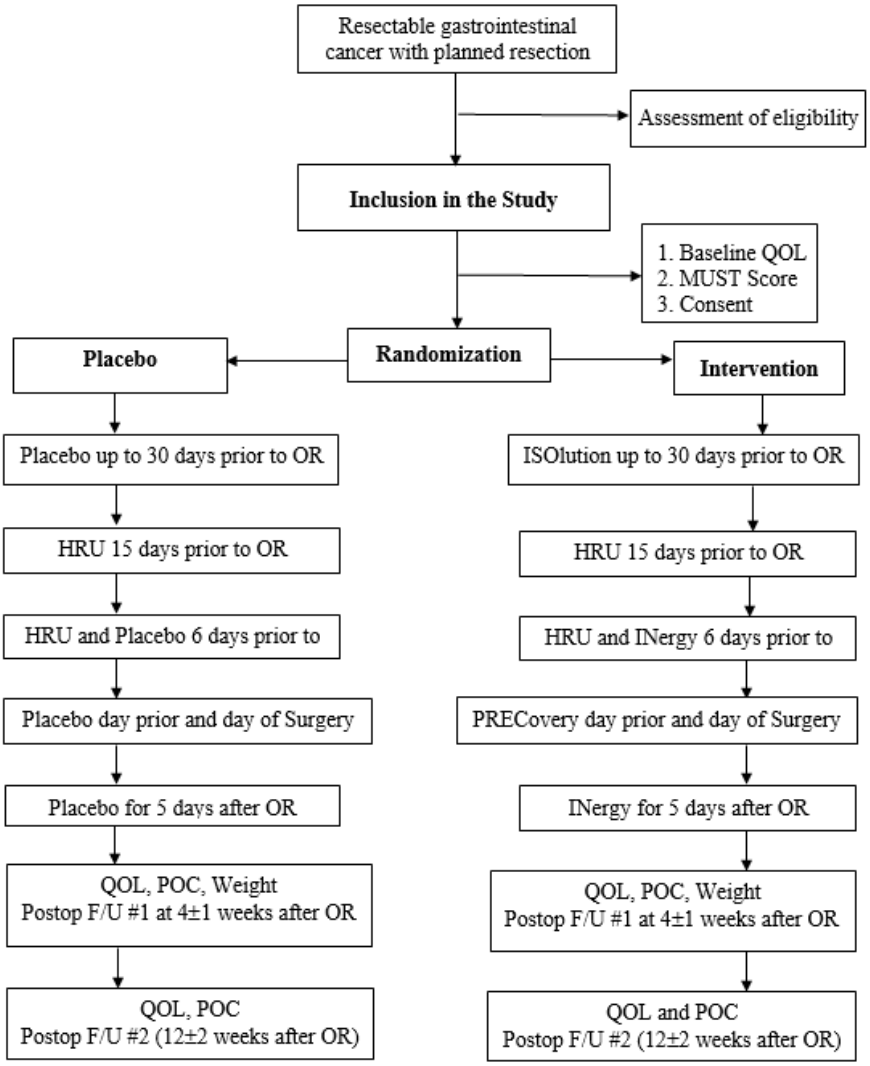
Patients will be asked to consume 1 serving of 20 g of protein isolate powder mixed in 250 mL of liquid or soft foods every day from the date of randomization to up to 6 days before surgery. Additionally, they will be asked to consume 3 servings of 51 g of an immune-modulating formula mixed in 250 mL of cold water for 5 days before and after surgery as well as 2 servings of 55 g of carbohydrate-rich powder mixed in 400 mL of cold water the evening before surgery and 1 serving 2-3 hours before anesthesia. Administration of the carbohydrate loading substance will be modified for patients following the Enhanced Recovery After Surgery (ERAS) Protocol. All study participants who are also taking part in the ERAS Protocol will be asked not to take the carbohydrate loading supplement as per the ERAS Protocol and will be asked to take the carbohydrate loading substance (or placebo) provided for this study. Routinely at our center, patients undergoing colorectal surgery are enrolled in an ERAS Protocol that encourages drinking fluids on postoperative day 1. Patients undergoing hepatobiliary surgery (either pancreas or liver surgery) are not included in an ERAS pathway; however, they are also encouraged to start a diet usually composed of liquids on day 1 after surgery. Patients undergoing gastric surgery are kept nothing per mouth for 7 days. However, they are started on tube feeds on day 1 after surgery.

At this point, patients will fill out a daily compliance diary from the date of randomization until up to 5 days after surgery. This compliance diary will be transcribed into a preoperative compliance case report form (CRF) that includes the number of packets the patient took every day, the volume that was ingested, the days it was ingested for, and the reasons patients were not compliant. While in the hospital, the nurses will be responsible for administration, as PReSS will facilitate the administration of the supplements (INergy-FLD) by adding them to the nursing care pathway of the patients. Compliance during this time will be obtained from the nurses' log, which includes the amount of solution the patient ingested during each administration and the days the patient ingested the solution. If for some reason, the patients are unable to tolerate an oral diet (postoperative complications such as delayed gastric emptying, ileus or bowel obstruction, etc), the nurse will contact the principal investigator of the study and the order to suspend the administration of the solution will be assessed for each patient. This will be noted in the nurses' chart and transcribed to the postoperative compliance CRF. Patients will continue to be part of the study.

Patient Follow-up

At the baseline visit, patients will have a complete history and physical examination recorded including height, current weight, and weight 6 months prior. Patients will complete a baseline QoL assessment during their clinic visit (Multimedia Appendix 1 and Figure 1). Patients will be asked to complete a health resource utilization form at 15 and 6 days before surgery (Multimedia Appendix 1). Immediately after surgery, patients will be followed on a daily basis during their hospital stay to collect postoperative complications and compliance data and length of hospital stay (Multimedia Appendix 1). Following discharge from the hospital, patients will then be assessed at their first postoperative clinic visit 4 weeks (±1 week) following the index surgery. The second postoperative follow-up will happen at 12 weeks (±2 weeks) following surgery. At each assessment, a physical examination will be completed. A QoL questionnaire will be given to patients to complete while they wait in the surgical clinics. They will also be asked to complete a health resource utilization form at each assessment. Mortality will be recorded 90 days after surgery.

Figure 1. Study schema. F/U: follow-up; HRU: health resource utilization assessment; MUST: Malnutrition Universal Screening Tool; OR: operating room (index surgery); POC: postoperative complication assessment; QoL: Quality of Life Assessment.



Data Management

In addition to physical examination and QoL data, a research assistant will gather postoperative complication data from patients' charts or electronic medical records and transcribe it on to CRFs, which will be updated daily while the patient is in the hospital. Before surgery, a compliance diary will be provided to patients to evaluate their adherence. Compliance data will also be collected from the nurses' charts while the patient is in the hospital, with a specific CRF designed to record the volume of the supplement the patient has taken after surgery. The feasibility CRF will include reasons for two different processes: (1) reasons for not consenting and (2) reasons for not randomizing if the patient consented. Data will be stored in a secured electronic database at OCOG.

Sample Size and Feasibility

Currently, there are 200 gastrointestinal resections performed annually for gastrointestinal cancer at JHCC (300 over an 18-month period). We expect at least 55.0% (165/300) patients to be eligible for the study. Additionally, we expect that 60.6% (100/165) eligible patients will be randomized to either intervention or placebo. Assuming a two-sided alpha of .05, this will give us a 95% CI around the estimate of 53.0%-68.0%. A sample size of 100 (50 per group) will enable us to estimate the treatment effect and corresponding variance of the complication rate, CCI, and QoL measures with adequate precision. Given the number of patients that undergo surgery at JHCC and the number of patients eligible for the study, we believe we can complete accrual to the study in 18-21 months. Given that the follow-up is 3 months, we expect the study to be finalized within 21-24 months of commencement.

Statistical Analysis

Patient baseline characteristics and demographics by treatment group will be presented using descriptive statistics. The proportion of eligible patients randomized and its corresponding 95% CI will be calculated using the Wilson method. The criterion for success of this study is defined as the proportion of eligible patients randomized as ≥60.0% (60/100). If the estimated proportion is <40.0% (40/100), the trial will be considered not feasible. If the proportion is between 40.0% (40/100) and 59.0% (59/100), the trial will be considered feasible, with modifications to improve enrollment.

The difference in the proportions of any postoperative complication between groups and its corresponding 95% CI

will be calculated using the Wilson method. The proportion of patients who are compliant with study therapy and 95% CI will also be calculated. Differences in compliance between treatment groups will be described. Good compliance will be defined as consumption of ≥70% (at least 41/58) sachets of the study intervention before and after surgery. If the compliance is ≥70% (at least 41/58 sachets), there will be no exploratory analysis to evaluate the reasons for noncompliance. Compliance of <70% (40/58 sachets or less) will be considered poor, and reasons for noncompliance will be further explored (eg, problems with the distribution or administration of the supplements, bad taste, side effects, inability to tolerate oral intake, etc) These reasons will be clearly stated in the compliance CRFs.

The mean (SD) of the CCI at 90 days from the index surgery will be estimated for each group, and the mean difference between groups will be estimated with its corresponding 95% CI. QoL scores will be summarized using means and corresponding SDs. The mean difference in the QoL scores between groups at 1 and 3 months will be estimated using linear models adjusting for baseline QoL scores.

Ethical Considerations

The study will be performed in accordance with the recommendations for guiding physicians in biomedical research involving human patients by the 18th World Medical Assembly, Helsinki, Finland, 1964. There are no perceived risks with respect to carbohydrate loading, protein solution, and immunomodulation solution as they are unlikely to interfere with cancer. The supplements being used are classified as food products, and as a result, there are no requirements in the Health Canada Food and Drug Regulations for this study. The Hamilton Integrated Research Ethics Board has approved the study protocol and documents prior to initiation. Written informed consent will be obtained from all patients prior to enrollment in compliance with International Conference of Harmonization and Good Clinical Practice guidelines and the REB.

Results

Primary Outcome

The primary outcome for each eligible patient will be defined as being randomized to intervention or placebo. The primary feasibility outcome will be one of the following: (1) stop, main study not feasible: estimated proportion of randomized patients <40.0% (40/100); (2) continue with protocol modifications: estimated proportion of randomized patients between 40.0% (40/100) and 59.0% (59/100); or (3) continue without modification: estimated proportion of randomized patients ≥60.0% (60/100).

Secondary Outcomes

The secondary outcomes of the study will be defined as follows:

1. Compliance: intake of at least 70% (41/58) sachets of study intervention volume.
2. Overall complications: occurrence of any postoperative complication (major or minor) from surgery following each patient's hospital stay and up to 90 days from the initial operation. Occurrence of any postoperative infections will also be calculated.
3. CCI at 90 days from the index surgery will be determined for each patient. This index can be calculated for each patient using the CCI Web-based calculator [26,30] following the grading of each postoperative complication according to the Clavien-Dindo classification [31].
4. QoL: The global health-related QoL at baseline, 1 month, and 3 months following randomization will be measured using the European Organization for Research and Treatment of Cancer Quality of life Questionnaire [32,33] instrument and the Functional Assessment of Cancer Therapy-General scale [34].
5. Length of hospital stay will be determined for each patient.

Compliance with the intervention is a secondary objective and will be taken into consideration for the success of its feasibility, as modifications to the protocol may be needed if compliance is poor. Compliance will be measured as the percentage volume of prescribed study intervention consumed, which will be measured by a patient diary in the preoperative period and nurses' charts in the postoperative period. Postoperative complications (major or minor) will be determined following each patient's hospital stay and up to 90 days from the initial operation. This is classified according to Clavien-Dindo classification [26,31,35].

Adjudication

An adjudication committee consisting of 2 experts in the field will review each patient's complications using deidentified source documents including discharge summaries, operative reports, interventional radiology reports, imaging reports, microbiology reports, and physician hospital and clinic progress notes as well as consultation notes from other physicians. The first adjudicator will review each complication, confirming that all reported complications are accurate, not duplicated, and appropriately classified. Whenever there is agreement with the site-reported outcome, then the outcome is considered confirmed. If there is a disagreement between the site and the first adjudicator, the second adjudicator will review that particular file. Any disagreement will be resolved by consensus, either by agreeing with the site or with the first adjudicator. Variables recorded include the length of hospital stay, blood work results, microbiology data, operating room time, estimated blood loss, number of blood transfusions during surgery and the hospital stay, and reoperations or readmissions. Each complication must be supported by source documents. The outcome assessment will follow the strict criteria set by Clavien-Dindo classification [26,31,35] and the CCI [26,31]. The outcome assessors will undergo adjudication training.

Adverse Events

The study will be conducted according to the International Conference of Harmonization and Good Clinical Practice consolidated guidelines. Currently, there are no foreseeable risks in administering nutritional supplements to patients who meet the eligibility criteria. Nutritional supplements are safe when used by adults as instructed [36,37].

Table 1. The study timeline.

Planned completion date	Study goals
December 2017-September 2018	Attain Initial Research Ethics Board Approval, receive initial shipment of the Nutritional Supplements and Placebo, and submit Research Ethics Board Amendments for approval required prior to recruitment
October 2018	Begin recruiting patients
July 2018	Have 50.0% (50/100) of participants enrolled in the study
April 2020	Complete study enrollment. Have 100% (100/100) of participants enrolled in the study
May-September 2020	Complete final follow-up visits
October-December 2020	Complete final statistical analysis and begin preparing manuscript
December 2020	Have final manuscript completed and ready for publication

If an adverse event (AE) occurs during the study and is deemed related to the administration of the study treatment, this will be reported using version 4.0 of the Common Terminology Criteria for Adverse Events (Multimedia Appendix 2) [38]. This data will be collected from the first administration of treatment until the last study visit.

The investigational food products are ISOlution (whey protein isolate), INergy-FLD (immunonutrition), and PreCovery (carbohydrate loading). AEs will be considered related to study product if they are deemed to be related specifically to the administration of ISOlution, INergy-FLD, or PreCovery.

Worsening of gastrointestinal cancer is expected and therefore will not be considered an AE for the purpose of this study. Deaths due to gastrointestinal cancer are outcome events and will not be reported as AEs.

Scientific Reporting and Publication

The Steering Committee is responsible for the scientific reporting, publishing, and presentation of the study results. All investigators participating in this study must agree to delegate the primary publication or presentation responsibility to the Steering Committee. Any other publication or presentation related to the study and the results by any investigator or participant must receive prior approval from the Steering Committee. No other publication or presentation is allowed before the primary publication or presentation by the Steering Committee. Authorship will be determined by the Steering Committee. The information developed during the conduct of this study is considered confidential.

The timeline for the study can be found in Table 1. We obtained research ethics approval from our local REB in December 2017. We aim to recruit 50 (100) patients of the patients by July 2019. The estimated study completion date is December 2020.

Discussion

Many patients in Ontario undergo surgery for gastrointestinal cancer each year. These surgeries are often associated with postoperative morbidity and infectious complications. Therefore, it is crucial to actively take steps to aid in recovery and improve patient QoL through perioperative optimization. Despite the debate on the role of perioperative nutritional supplements in improving postsurgical outcomes, we feel there is enough clinical interest in the surgical community to support a well-designed, randomized controlled trial addressing this question. The study will provide quality preliminary evidence for perioperative nutritional supplements and determine the feasibility of recruitment, randomization, and compliance, thereby providing the necessary information to design a phase III trial if the results of the study are favorable.

Acknowledgments

The study was funded by the JHCC Foundation.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Schedule of study procedures.

[PDF File (Adobe PDF File), 36KB - resprot_v7i10e10491_app1.pdf]

Multimedia Appendix 2

Common terminology criteria for adverse events (CTCAE) v4.0.

[PDF File (Adobe PDF File), 28KB - resprot_v7i10e10491_app2.pdf]

Multimedia Appendix 3

Peer-review report.

[PDF File (Adobe PDF File), 558KB - resprot_v7i10e10491_app3.pdf]

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Abbreviations

AE: adverse event
CCI: Comprehensive Complication Index
CRF: case report form
DHA: docosahexaenoic acid
ERAS: Enhanced Recovery After Surgery

FLD: formulated liquid diet
IL: interleukin
IT: information technology
JHCC: Juravinski Hospital and Cancer Centre
MUST: Malnutrition Universal Screening Tool
OCOG: Ontario Clinical Oncology Group
PReSS: Pharmacy Research and Support Services
QoL: quality of life
REB: Research Ethics Board
Th: T helper

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Protocol

Gamified Cognitive Bias Interventions for Psychiatric Disorders: Protocol of a Systematic Review

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Abstract

Background: Cognitive bias modification has been increasingly studied in the past decade with reviews reporting the effectiveness of bias modification. Advances in electronic health and mobile health technologies have transformed how conventional cognitive bias modification is delivered. To date, gamification technologies and serious games have been widely evaluated in health care, and prior studies have reported the use of gamification for cognitive bias modification. However, no prior research, to date, has systematically evaluated the literature for gamified cognitive bias modification interventions.

Objective: The proposed systematic review aims to review how gamification has been applied to cognitive bias modification interventions.

Methods: A systematic review will be conducted. A search will be conducted on the respective databases till 2018. Selection of the studies will be determined by the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Quality assessment of the included studies will be assessed using the Cochrane Risk of Bias Tool. In addition, a narrative synthesis will be conducted.

Results: We expect that the review will be completed 12 months from the publication of this protocol.

Conclusions: The findings that arise from this review will be crucial as they will inform future research that seeks to integrate gamification technologies into existing conventional bias modification interventions.

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KEYWORDS

attention bias; cognitive bias; gamification; eHealth; mHealth

Introduction

Background

Gamification refers to the usage of game-designs features in nongame contexts [1]. In comparison, serious games refer to games that are explicitly created for nonrecreational purposes and are designed specifically for education, training, or behavioral modification [2]. Gamification, thus, differs from serious games, in that the main objective of gamification is in the creation of a game-like experience through the incorporation of various gaming mechanics and design. Some of the common gaming techniques include that of digital rewards, avatar, competition, social pressure, feedback, levels, achievement ranks, leaderboards, and three-dimensional environments [1]. Essentially, the main objective of introducing gamification elements is aimed at making interventions more engaging, enjoyable, and motivating for participants. Incorporating gaming elements changes the interaction between the individual and the app and might result in increased self-empowerment. Based on prior studies, it is known that gamification not only helps individuals to better engage with the intervention but also helps to increase individuals' intrinsic and extrinsic motivation for

intervention [3]. In addition, in some instances, gamification helps to improve skill sets and provides individuals with social support [3].

To date, gamification technologies and serious games have been widely evaluated in health care. Sardi et al [3] undertook a prior systematic review of gamification in electronic health and synthesized the evidence from 46 prior studies. Their review highlights that most of the current interventions are in the domains of chronic disease rehabilitation, physical activity, and mental health [3]. In addition, gamification, in the current context, serves mainly to be an extrinsic motivator for individuals [3]. Lau et al [2] in their recent meta-analytical study reviewed the evidence for serious games for psychiatric disorders. Based on their identified studies (10 studies, with studies involving the delivery of serious games through a computer), it was reported that serious games helped in the improvement of various psychiatric symptoms, with an effect size of 0.55, compared with controls [2]. While Lau et al's prior review was limited to that of serious games and not specifically gamification approaches, it helps to demonstrate the potential effectiveness if gaming elements are included. Lumsden et al's [4] review synthesized the current evidence for gamification, specifically for cognitive assessment and cognitive training. The authors, in their review, identified a total of 33 studies involving >31 gamified tasks and reported that researchers have considered gamification mainly to improve short- and long-term engagements and to make the task more attractive and potentially increasing the effect of cognitive training. Lumsden et al [4] recommended for there to be further validation of gamified tasks against a standard cognitive task and for studies to have the appropriate sample size, to better distinguish the effects of gamification on task performance. Of included studies in Lumsden et al's [4] prior review, one focused on a specific form of cognitive retraining—attention bias modification. We will provide an overview of cognitive bias modification, the evidence for cognitive bias modification, the use of gamification technologies for cognitive bias modification, and define the rationale for this review.

Cognitive bias modification has been increasingly studied in the past decade. Cognitive biases include that of attention, approach or avoidance, and interpretative biases. Attentional biases refer to the preferential allocation of attention toward stimuli that are high in salience [5,6]. Closely related to attention biases are that of approach biases, which refer to automatic tendencies to reach out and approach stimuli with high salience [7]. In contrast, interpretative biases tend to result in individuals making negative evaluations of an ambiguous situation [8]. These biases have been posited to be involved in the psychopathologies of several psychiatric disorders, including anxiety disorders, alcohol use, and tobacco use disorders [9-13]. The presence of these biases implies that they could be subjected to manipulation and modification. Commonly, tasks such as that of the visual probe have been used for the modification of attention biases, and this involves the pairing of probes with the neutral stimulus (words or images) 100% of the time to retrain biases away from substance cues [14]. Tasks like the approach or avoidance are used for bias modification, by presenting cues in the push-away format and the neutral cues in a pull-closer format [15]. For modification of interpretations, this involves presenting individuals with ambiguous scenarios and with word fragments that help to disambiguate the scenarios positively [16]. There have been reviews conducted to date (Cristea et al [8] and Jones et al [17]) that have provided evidence pertaining to the overall effectiveness of bias modification. Cristea et al [8] identified trials including participants with alcohol or tobacco use disorders (25 trials) [18] in their review and reported that bias modification for both attentional and approach biases was moderately effective, with an effect size of 0.60 (Hedge 0.60) [19]. Despite there being changes in cognitive biases, the authors reported that there was no overall change in other symptomatology, such as that of cravings. The findings that Cristea et al arrived at might have been limited by the fact that they synthesized both clinical and nonclinical trials together, as highlighted by a commentary published in response to their meta-analysis. Jones et al [17] in their meta-meta-analyses found that cognitive bias modification was most effective or anxiety disorders, with the effect size for anxiety disorders ranging from 0.13 to 0.74 [17]. In addition, they reported the effect sizes of cognitive bias modification for depressive disorders to range between 0.35 and 0.85 and for appetitive disorders (defined to include eating disorders and addictive disorders) to range from 0.003 to 0.36 [17].

One of the main limitations of cognitive bias modification has been that the intervention has conventionally been confined to that of a laboratory, but that has changed in recent years. The advances in internet and mobile technologies led to these technologies being used for the delivery of cognitive bias modification. Wiers et al [20] administered the attention control training and approach bias retraining intervention using the internet among 136 problem drinkers and found a reduction in drinking across all intervention groups, even in the control group. In another study, William et al [21] delivered a Web-based cognitive bias modification training targeting imagery and interpretation bias among depressive individuals and found that the Web-based combined intervention (cognitive bias modification for interpretations together with internet cognitive behavioral therapy) was effective in reducing depression symptoms and distress symptoms, with an effect size (Cohen *d*) of 0.62-2.40. In particular, 27 participants had a clinically significant reduction in their symptoms following bias modification. These pioneering studies highlight the potential of bias modification delivered using the internet. The rapid advances in mobile health technologies have led to a further transformation of attention bias modification programs, as such mobile technologies are also being harnessed in the delivery of bias modification interventions. Clarke et al [22] reported that a mobile attention bias modification task was useful in helping to reduce the sleep-related threat, cognitive arousal, and help to improve insomnia symptoms; this was supported by electrophysiological measures that demonstrated that those who underwent the bias modification had better sleep quality. Apart from changes in the delivery mechanism for cognitive bias modification, a growing interest in gamification technologies has led to such technologies augmenting cognitive bias modification. For example, Dennis and O'Toole [18] reported how a single session of a gamified attention bias

modification task was effective in reducing subjective anxiety and stress reactivity.

Boendermaker et al [23] in their prior review explored how gamification could help to address some of the issues of conventional bias modification tasks, particularly that of the motivation to train, given how repetitive bias modification interventions are; in addition, they highlighted several gamification approaches specifically for cognitive bias modification interventions and explored how published works have utilized some of these approaches. While Boendermaker et al's [23] review provides a timely insight into how gamification strategies have been adapted for bias modification interventions, their review was not a systematic review, and no databases search was performed. There remains, to date, no prior research that has systematically evaluated the literature for gamified cognitive bias modification interventions. There is a need for evidence synthesis of these studies, for there to be an understanding of the effectiveness of a gamified approach for bias modification. Hence, this review is timely. Findings that arise from this review will be crucial as they will inform future research that seeks to integrate gamification technologies into existing conventional bias modification interventions.

Research Aims

The proposed systematic review aims to review how gamification has been applied to cognitive bias modification interventions. We hope to address the following questions through this review: (1) What domains has gamification been applied in for cognitive bias modification interventions; (2) What is the effectiveness of gamification as applied to cognitive bias modification interventions? This will be assessed for by means of determining whether (1) there has been any motivational improvement over nongamified interventions; (2) there are changes in the bias scores; and (3) there is improvement in other secondary outcomes (eg, improvements in terms of anxiety or depression scores or a reduction in the total amount of alcohol consumed).

A systematic review will be undertaken to achieve the objective of this review. Studies identified will be reviewed by independent assessors and screened against our predefined inclusion and exclusion criteria. The Cochrane Risk of Bias Tool will be used for the assessment of the risk of biases in randomized trials that have been identified. Furthermore, the evidence will be synthesized using qualitative synthesis.

Methods

Search Strategy

To identify the relevant papers, the following search terminologies will be used: ("cognitive bias" OR "attention bias" OR "interpret* bais" OR "approach bias" OR "avoidance bias") AND ("training" OR "modification" OR "practice" OR "therapy") AND ("gamification" OR "game elements" OR "game" OR "gaming" or "Game mechanics"). The following databases will be searched: PubMed, Medical Literature Analysis and Retrieval System Online, PsycINFO, Science Direct, Scopus, EMBASE, and Cochrane CENTRAL. Databases will be searched from the year 2000 onwards to current, as prior to the year 2000, there were limited computer-based interventions. The search strategy will be modified for different databases. If full-text access is not available, the original authors will be contacted for their papers.

Inclusion and Exclusion Criteria

Only English language papers will be included in this review. The inclusion criteria are as follows: (1) papers must describe a cognitive bias modification intervention; (2) the intervention utilized needs to be a novel gamified-like task; (3) papers included must be randomized studies; (4) participants must have underlying psychopathological symptoms; and (5) there needs to be a control or comparison group for comparison.

Papers will be excluded if they fulfill the following exclusion criteria: (1) papers are reviews, opinion pieces, or design documentations; (2) the intervention utilized is that of an existing over the shelf intervention; and (3) papers are nonrandomized studies.

Condition or Domain Being Studied

This review will focus on all psychiatric disorders.

Participants

Participants could be individuals recruited from either the community of from a treatment facility. Participants could be adolescents or adult participants. Participants need to have existing psychopathological symptoms (such as that of affective conditions). Participants do not need to be formally diagnosed with a psychiatric condition.

Intervention

The intervention in this case is that of a cognitive bias intervention task, which could be that of the visual or dot-probe task and cognitive bias modification for interpretations.

Comparisons

Participants will be compared with other participants who have received either treatment as usual or placebo or sham training.

Outcome

For the outcome, the main (primary) outcome would be whether the gamified intervention has been effective, and if effective, the effect size for the intervention. For the secondary outcome, we will report if there is a reduction in the symptoms of specified psychiatric disorders and motivation to train or use the app.

Data Extraction, Sorting, and Selection

All papers will be screened on the basis of their titles and abstract by two independent authors. Full copies of the shortlisted papers will then be evaluated against the inclusion and exclusion criteria. Any disagreement between the two authors will be resolved using discussion with the third author. An electronic document will be utilized to record systematically the reasons for inclusion and exclusion of each of the paper. This review will adhere to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols.

The following data will be systematically extracted from each paper and recorded on a standardized electronic data collation form and cross-checked by another independent assessor:

1. Publication details: authors(s) and study year
2. Study design and methods: study design, sample size, type of sample (treatment seeking or community cohorts), country in which study was conducted, demographics of the sample, diagnosis of participants, and methods using which diagnosis is made
3. Method of attention bias assessment and modification
4. Primary outcome: effectiveness of gamified attention bias modification
5. Secondary outcome: severity of underlying psychiatric condition and motivation to train or use the app

Quality Assessment

The risk of bias assessment will be assessed by means of the Cochrane Collaboration Risk of Bias tool for randomized trials [24].

Strategy for Data Integration or Synthesis

For this review, we will perform a narrative synthesis of the evidence. We will provide a summary of the domains or conditions in which gamification has been applied for cognitive bias modification. We will summarize the number of studies reporting the effectiveness of cognitive bias modification interventions. We will summarize and synthesize the evidence pertaining to the effectiveness. In addition, we will summarize the findings from all studies pertaining to whether there was a motivational improvement and whether there has been an improvement in other secondary outcomes reported.

Results

We expect that the review will be completed 12 months from the publication of this protocol. We will report the results based on the identified outcomes as specified above.

Discussion

Principal Findings

To the best of our knowledge, this is the first planned study that will review the status of gamified cognitive bias modification interventions for psychiatric disorders. This planned review addresses the limitations of prior reviews, given that none of the prior studies has systematically evaluated the literature for gamified intervention. There is a need for evidence synthesis, as the evidence synthesis will help inform us about the types of psychiatric disorders that such features have been applied to. In addition, this review will help us in determining whether the gamified interventions have their basis on conventional cognitive bias modification tasks, such as that of the Stroop, visual probe, or cognitive bias modification for interventions. More importantly, the review will help us in the identification of common gaming elements that have been incorporated in published gamified interventions. This is of importance as it will help guide further research that would seek to develop a new gamified intervention for other forms of psychiatric disorders. If gamification is found to be effective in only some studies, this implies that there needs to be careful consideration of the appropriate gamification strategies to adopt.

Conclusions

The findings that arise from this review will be crucial as they will inform future research that seeks to integrate gamification technologies into existing conventional bias modification interventions.

Conflicts of Interest

None declared.

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Protocol

Facilitating the Informed Consent Process Using Teleconsent: Protocol for a Feasibility and Efficacy Study

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Abstract

Background: Informed consent is among the biggest challenges in recruiting participants for clinical research studies. Researchers face many challenges in conducting clinical trials, some of which include budgetary restrictions, lack of trained personnel, and difficulty recruiting study participants—particularly minorities and participants from rural communities.

Objective: The objective of this study is to utilize telemedicine to improve the informed consent process for clinical trials and studies. We aim to assess the feasibility and efficacy of the teleconsent intervention among residents in urban and rural settings.

Methods: This study will be conducted separately yet concurrently at two institutions, the Medical University of South Carolina and the University of North Carolina at Chapel Hill, to compare results within and across institutions.

Results: Enrollment for Phase 1 began in March of 2018 and concluded in May 2018. Data transcription and analysis will be conducted through June and September of 2018.

Conclusions: In this paper, we present a novel approach for conducting informed consent using a new telemedicine modality, namely, teleconsent. Teleconsent presents the ability to conduct a live interaction among clinical research coordinators and potential participants while synchronously presenting the consent form on the screen and obtaining participant's signature through doxy.me, the teleconsent system. Teleconsent provides potential to improve obtaining informed consent from potential clinical trial participants.

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KEYWORDS

telemedicine; informed consent; clinical trials; mobile phone

Introduction

Challenges Obtaining Consent for Research

Researchers face many challenges in conducting clinical trials, some of which include budgetary restrictions, lack of trained personnel, and difficulty recruiting study participants—particularly underserved and participants from rural communities [1]. Failure to meet enrollment goals can lead to a considerable amount of research waste, including costly time extensions [2,3], underpowered study results, and unpublished results as well as study termination and costing research institutions and sponsors a substantial investment in both money and time every year. Moreover, an ongoing concern in clinical trials is the typical underrepresentation of underserved individuals of a population [4], some of whom may lack the means for transportation to the study site but may have access to mobile devices, smartphones, or community centers (eg, public libraries or coffee shops) where the internet and computers are available [5]. This underrepresentation of underserved individuals could hinder the generalizability of study results and the translation of knowledge and potentially

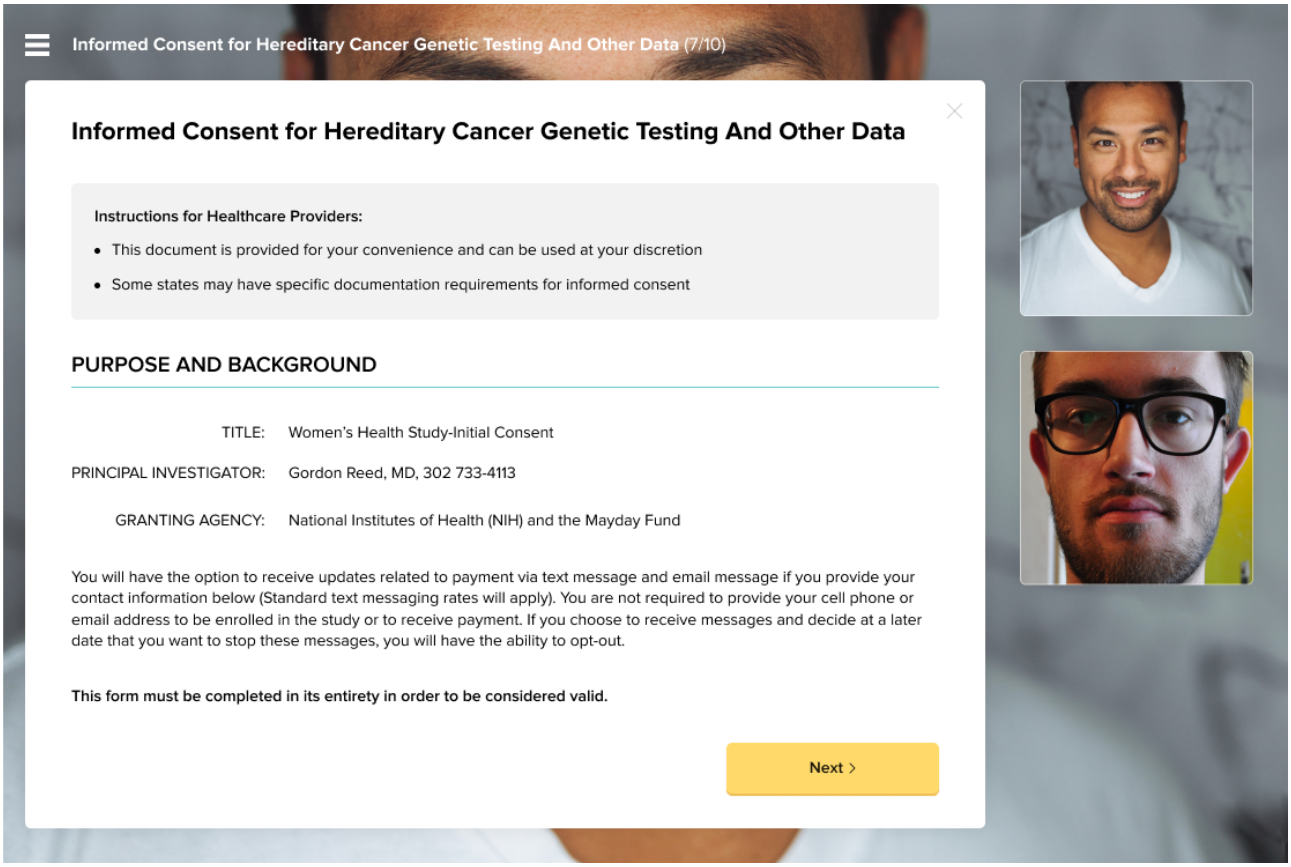
life-saving interventions into the routine clinical practice [4,6-9]; therefore, innovative approaches to increase access, improve participants' experience, and increase trust to research studies are needed [10-12].

Multisite and offsite clinical trials often impose considerable travel costs and time commitments on participants [13]. The consenting process is often performed in-person with participants visiting with study personnel before, during, or after their clinical visit. In multisite clinical trials, consent often requires faxing or mailing of documents to the coordinating site [12]. In addition, training of clinic staff to maintain the regulatory compliance can add to the burden of study participation. Finally, as direct-to-patient recruitment sites and other nontraditional, novel recruitment approaches increase in popularity [14], the current informed consent process will be difficult, if not impossible, to scale. Informed consent readability and comprehension continue to be a major issue; a participant's understanding during the consent process cannot easily be assessed by telephone or obtaining consent through an Web-based form [15,16]. The growing complexity of clinical studies and trials and the need to integrate trials into routine care (ie, the national movement toward more pragmatic clinical trials supported by the National Institutes of Health and the Patient-Centered Outcomes Research Institute, in particular) demand more accessible solutions for eliciting consent [17].

Teleconsent as a Solution

The Biomedical Informatics team at the Medical University of South Carolina (MUSC) has developed "teleconsent," an innovative, informed consent approach that leverages telemedicine technology to conduct remote, live consent sessions between participants and researchers. Teleconsent allows research personnel to meet and discuss the study with a prospective participant virtually using a video feed, share an informed consent document that can be collaboratively filled out by a participant and study personnel in real time, and generate an electronically signed informed consent document (Figure 1) available for immediate PDF download or print by both parties. This process can eliminate the inefficiencies related to travel, time, and management of personnel at remote sites [18]. In addition, the addition of a telehealth session will provide visual cues that may help research staff evaluate a potential participant's understanding of risks, benefits, and other important elements of consent. New e-consent technologies may overcome some of the challenges related to comprehension by adding multimedia and interactive sessions testing participants' comprehension [19]. To these tools, teleconsent adds opportunities for enhanced communication and remote access. Preliminary results, pilot studies, and anecdotal feedback regarding teleconsent have shown that participants are generally highly satisfied with teleconsent and did not experience difficulties understanding and navigating teleconsent and the process itself; however, there was a moderate, inverse relationship between age and satisfaction [20].

Figure 1. A mock consent form displayed in the Doxy.me software during a live teleconsent session.



Need for This Research

We are conducting a study that evaluates participants' reactions to the teleconsent software, including their feelings regarding privacy and ease of use. We have 3 main objectives. First, we seek to understand the feasibility of using telehealth in rural areas, acceptability among underserved populations, and ethical and privacy concerns of using the teleconsent software and remote communication through participant interviews, particularly among minorities, rural, and elderly participants aged >65 years. Second, we aim to evaluate the quality of informed consent by comparing participants' perception and comprehension using either teleconsent or paper-based consenting in ongoing clinical studies, through partnerships with investigators conducting those studies, by assigning participants to either teleconsent or traditional paper-based consenting. In addition, we will determine to what extent, if any, the teleconsent process affects participants' informed consent and the workflow of research staff conducting the studies. Third, we intend to assess the workload on research assistants and their perception of the usability of teleconsent in terms of ease of use and user friendliness of the interface.

Methods

Study Setting

Study procedures will be conducted concurrently at 2 institutions, the MUSC and the University of North Carolina at Chapel Hill (UNC) to compare results both within and across institutions.

Study Overview

This study is divided into 2 phases, to be completed in subsequent order and concurrently at both study sites. Phase 1 aims at meeting the first objective by conducting remote mock consent sessions using the Doxy.me software (Figures 1 and 2) and through interviewing participants about their experiences, preferences, and concerns with the technology, processes, and privacy.

In the second phase, we will complete our second and third objectives by partnering with ongoing clinical trials and assigning participants to either teleconsent or traditional paper-based consenting and then assessing the quality of informed consent and workload, among other metrics; of note, this part of the study will be initiated in the winter of 2019. Full procedures for both study parts are outlined in the "Procedures" section of this paper.

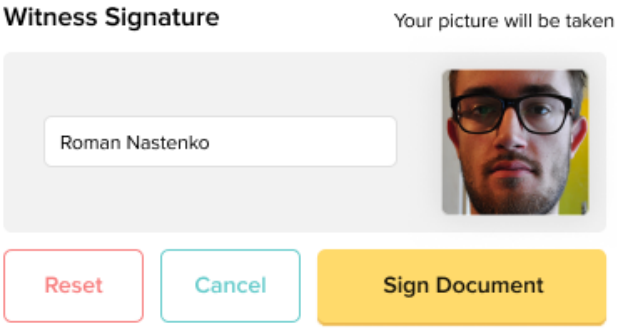
Eligibility Criteria

For phase 1, prospective participants are required to be, at least, 18 years of age, currently residing in North or South Carolina, speak English as their first language, and have access to the internet and a computer with a microphone and camera. Any participant who does not meet the inclusion criteria will be excluded from the study. Our decision to exclude participants who do not reside in North Carolina is because one goal of this software is to study how North Carolina residents react to the software and compare the data to that of our MUSC. In addition, we choose to exclude participants who do not speak English as their first language to control for potential language barriers in this feasibility study. Moreover, the technological requirements of Doxy.me require participants to have access to a laptop or desktop with the appropriate audio-video capabilities; notably, the software was not compatible with tablets, such as iPads, or smartphone at the time of this publication. For phase 2, the eligibility criteria for our study is the same as those for the clinical trial sites.

Recruitment

Each study site will have a unique recruitment process. For phase 1, in South Carolina, participants will be recruited through the dissemination of Institutional Review Board flyers placed in clinical and community settings and distributed by our Community Advisory Board members, advertisements, word-of-mouth, and at community-based clinic sites. Participants at UNC will be recruited through a researcher-participant networking website called Join the Conquest, word-of-mouth, and direct participant recruitment at Broad Street Clinic in Morehead, North Carolina. In addition, participants' recruitment at UNC will be facilitated by 2 research assistants, the principle investigator and coprinciple investigator, and the staff at Broad Street Clinic. At MUSC, recruitment will be facilitated by the research coordinator. Both institutions will implement a prescreening eligibility questionnaire. On Join the Conquest, persons interested in the study will be directed to a Qualtrics eligibility survey, which will include demographic information. At MUSC, surveys will be completed through the Research Electronic Data Capture Platform (REDCap) [21]. From the pool of prospective participants obtained, we will select a total of 40 through a screening process that will be detailed later. Chosen participants will be offered gift cards or cash as remuneration.

Figure 2. The teleconsent software allows the research coordinator and participant to sign the consent form in real time electronically.



For phase 2, participants will not be directly recruited for our study. Instead, we will partner with investigators conducting ongoing clinical research and assign those study participants to use either teleconsent or traditional paper-based consenting for the informed consent process. In total, 64 patients and up to 10 research assistants will be involved in this part of the study at the UNC site, though the number of research assistants may be as low as 2. Patients will be paid each time a set of surveys are completed. Research assistants will be paid upon the completion of each National Aeronautics and Space Administration (NASA)-Task Load Assessment (TLX) form (to be completed after each consent session) and also upon the completion of each System Usability Scale (SUS; to be completed approximately 3 times throughout the study). In addition, research assistants will be paid for participation in a focus group.

Screening

For phase 1, participants' screening will occur through the Qualtrics or REDCap surveys or over the phone. The demographic information collected during the screening process (age, gender, race, ethnicity, and county) will be used to select a group of participants who are coming from a variety of backgrounds to study potential differences between reactions to teleconsent among various demographic groups. For phase 2, participant screening will not occur.

Randomization

No randomization will be involved in phase 1. For phase 2, if the parent study permits, participants will be either randomly assigned to each of teleconsent or traditional consent. When random assignment is not possible, for example, in studies in which some participants do not have the option of being assigned to traditional consent, thereby negating random assignment, we will use the propensity score matching after assignment to either teleconsent or traditional consent. Once verbally consented through one of these means, participants will undergo the informed consent process.

Procedure

In phase 1, following the initial eligibility screening and identification as possible participants, interested individuals will be contacted by emails or phone to invite them to schedule a 1-hour mock consent session with a member of the study team. Before the mock consent session, participants at UNC will e-sign an Web-based consent form sent by Qualtrics and those at MUSC provide verbal consent at the time of scheduling, which is confirmed by the coinvestigator prior to participating in study procedures. During the mock consent session, study personnel will give participants a brief overview of Doxy.me and teleconsent before walking participants through a mock consent form created for this study. The purpose of the mock consent form is not to actually complete an informed consent session but to highlight the functionalities of the software. Immediately after the completion of the mock consent process, study personnel will conduct audiorecorded, semistructured interviews with participants about their experiences. After the study completion, participants will either receive cash or a gift card sent electronically or mailed to their residence(s). In total, 40 participants are to complete phase 1 of the study at each site, for a total of 80 participants between UNC and MUSC.

For phase 2, participants (n=64 at each site) will be assigned to either consenting for the clinical trial through teleconsent (n=32) or through paper-based consenting (n=32). Notably, 64 subjects per site (totaling n=128 between sites) will provide 80% power to detect modest differences (effect sizes ~0.50) between groups with respect to the survey instrument scores. After consenting for participation in the teleconsent study, participants will undergo the informed consent process using either teleconsent or traditional consent. After the completion of the consent process, participants will immediately fill out the quality of informed consent (QuIC), Decision-Making Control Instrument (DMCI, and Short Assessment of Health Literacy-English version (SAHL-E). Thirty days postconsent, participants will be asked to fill out this set of surveys once more electronically; they will be paid for each set of surveys completed.

Study personnel who are consenting potential participants will fill out a NASA-TLX form for each patient; they will be paid for each form filled. In addition, they will fill out SUS 3 times throughout the study, once at the beginning of their participation, once toward the middle, and once after they have completed enrolling participants for the teleconsent study; they will be paid for each SUS filled out. Finally, after the termination of the teleconsent partnership, those who will be obtaining informed consent for these studies and will assist in the collection of instruments will be invited to participate in a focus group asking about their workload and perceptions of the Doxy.me software for teleconsent. Focus group participants will be receiving remuneration for completing the focus group.

Study Instruments

We will use the cognitive interviewing technique of verbal probing adapted from Willis to evaluate comprehension, decisions, and voluntariness, as proxies for users' trust and intention to complete trials using the DMCI [22] and the QuIC [23] tool.

It is important to evaluate the decisional capacity and comprehension in informed consent processes, and research has identified that individuals with lower educational levels, mental illness, and advanced age are at risk of lower comprehension and potentially can be misled regarding the intent of the research [24]. To evaluate this, we will use the DMCI, a validated instrument that has been used to assess voluntary consent. The DMCI has a demonstrated internal consistency of 0.83 in psychometric studies [25]. The 9-item DMCI is used to assess perceived voluntariness, trust, and decision self-efficacy; in addition to a total score, it contains subscales addressing self-control, absence of control, and others' control. In addition, the QuIC, a validated instrument that measures subjects' understanding of the consent process in clinical trials and therapeutic misconception [23], is used to assess comprehension. The QuIC was designed to measure the actual (objective=20 items) and perceived (subjective=9 items) understanding of cancer clinical trials and can act as a screen for disclosure and capacity. The intraclass correlation coefficients (test-retest reliability) of.77 have demonstrated the reliability of this tool. We use the SAHL-E tool to measure health literacy. SAHL-E

is an 18-item instrument that includes distractors on various health items, takes approximately 2 minutes to administer, and has a reliability of.89 [25].

In addition, validated surveys will be provided to all study personnel engaged in this process at the clinical trial sites to evaluate their level of satisfaction and workload experienced (NASA-TLX Task Index Scale) with the recruitment process [26,27]. NASA-TLX is a subjective workload assessment tool, which allows users to perform subjective workload assessments on operators working with various human-machine systems [26,27]. Using various metrics, including the QuIC tool [22], DMCI [23], SUS, the Doxy.me system through the NASA-TLX, SUS, and focus groups.

Study Design

The design of phase 1 of our study is a qualitative study with a semistructured interview format. The ethical approval was obtained from the Institutional Review Boards at the UNC (17-2769) and the MUSC (# Pro00068715).

The design of phase 2 of our study is a 2-arm, teleconsent study, which assesses various metrics using standardized surveys. The ethical approval was obtained from the Institutional Review Board at the UNC (17-2870).

Data Management

Survey assessments and demographics will be collected through UNC Qualtrics survey, REDCap survey, or pen-and-paper. Interview audios will be recorded using a handheld device (following participants' consent) and stored on a secure MUSC Box server.

Data Analysis

In phase 1, all interviews will be professionally transcribed and imported into the NVivo 12.0 (QSR International Pty, Doncaster, VIC, Australia) qualitative analysis software. Verification of the transcript accuracy will be performed prior to analyzing the text. An iterative process will be used in the analysis of the data. Then, 2 team members will code the data following its transcription by tagging segments of text in the transcripts to a concept, expanding, refining, and reducing the concepts, and discussing the findings in detail to allow for cross-validation of findings between the 2 sites [28]. A coinvestigator at MUSC with advanced training in research ethics and bioethics will explore the ethical appropriateness and associated principles of teleconsent using an integrative bioethical approach, and the MUSC research team will review emerging findings at the midpoint and conclusion of coding to consider what additional data will be necessary to refine our understanding of the participants' perspectives related to teleconsent and determine overall themes. In addition, any feedback about the Doxy.me software will be submitted to developers at MUSC.

In phase 2, for patient participants, descriptive statistics (means, SDs, medians, etc) of responses to the survey instruments will be used to characterize the 2 groups (ie, teleconsent vs paper-based consent). Participants will be stratified with respect to demographics and clinical study. Each of the survey instrument summary scores and subscale scores will be essentially continuous variables; as such, comparisons between groups will be delineated through analysis of covariance modeling. In these models, the instrument score will serve as the dependent variable, with the experimental group serving as the key independent variable of interest. The analysis of covariance model includes participant factors, such as education and other demographics, as covariates in the models.

For study personnel, descriptive statistics will be used to study the differences in the NASA-TLX between the 2 groups through a 2-sample *t* test of means. The sample size of the research assistant group will be based on the number of research assistants currently working on the clinical trials. Regardless, we will assume 2-sided hypothesis testing with an alpha level of.05. We suspect that the null hypothesis will display no significant difference in the means of the research assistants' NASA-TLX scores for teleconsent versus paper-based consenting.

Results

Timeline

Enrollment and data collection for phase 1 is expected to conclude by December 2018. Data transcription and analysis will begin in January 2019. For phase 2, 2 clinical trials have been identified for a potential partnership, and these sites have modified their Institutional Review Board protocols to include the addition of teleconsent. Phase 2 will also begin in January 2019. We anticipate reporting results in June 2019 through professional presentations and publications. Study findings will be disseminated through publications, direct update to Community Board Members, and electronically to participants.

Dissemination

The results of the work from the above aims will be disseminated, throughout the Clinical Translational and Science Award (CTSA) consortium and the broader translational research community, through presentations at national meetings, such as the American Medical Informatics Association Translational Science Summit, relevant CTSA domain task force or interest group meetings, and through publication in peer-reviewed journals. The initial strategy for teleconsent is dissemination through academic research organizations in regional MUSC collaborations, including the Carolinas Collaborative and Mid-South Clinical Data Research Network. The teleconsent underlying framework, Doxy.me is a freely available lightweight telemedicine framework, which will facilitate the dissemination across the CTSA network.

Discussion

Telemedicine is an innovative health care delivery model that provides care to patients at a distance using telecommunications capabilities [29]. Telemedicine has gained substantial support in recent years as an acceptable care methodology, with effective utilization in many clinical domains that has the potential to overcome several gaps and barriers in clinical trial enrollment by having the ability to remotely recruit and consent potential research participants, especially rural participants who are outside the proximity of the study team. Thus, teleconsent offers a convenient and complementary solution for researchers to

meet with prospective participants and obtain consent. Researchers at the MUSC, partnered with the UNC, are interested in building off preliminary research focusing on the teleconsent software, Doxy.me, through a 2-part study.

In phase 1 of this study, participants will be recruited; participants will be residents of South and North Carolina (N=80; 40 from each respective site) from various backgrounds; however, all will meet the inclusion criteria specific to this study. Participants will be walked through the teleconsent process using a mock consent form and then interviewed to determine the overall themes regarding issues such as software difficulties and privacy issues. Results from this part of the study will be used to provide feedback to developers at the MUSC and address potential issues before phase 2, which will be completed in the summer of 2019. In addition, it will provide data on participant preferences, acceptability, and potential barriers to the adoption of teleconsent. For phase 2, researchers partner with ongoing clinical trials and assign participants (n=64 at each site) to either consenting by teleconsent or traditional paper-based consenting. Various validated surveys will be given to participants both immediately after the consent process and 30 days postconsent to determine differences in the understanding of the consent process between groups. Moreover, surveys will be administered to the study personnel who are consenting patients throughout the process to study the additional workload and demand placed upon them. We hypothesize that there will be no significant difference in the quality of informed consent or additional workload demand placed on researchers between traditional paper-based consenting and teleconsent. With these results, we hope to increase the usage of teleconsent in clinical trials to reduce barriers to study enrollment and improve underserved groups' participation in research.

Acknowledgments

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Conflicts of Interest

BW, a member of the MUSC team is the Founder and Chairman of Doxy.me, LLC. BW has not been involved in the planning or analysis of the research. He has not been involved in the recruitment or consenting of participants. BW's role on the project is to provide technical support and lead further software improvement cycles on Doxy.me and the teleconsent platform.

Multimedia Appendix 1

Notice of Award for Grant funding from NIH.

[PDF File (Adobe PDF File), 112KB - resprot_v7i10e11239_app1.pdf]

Multimedia Appendix 2

Summary statement and peer-review comments.

[PDF File (Adobe PDF File), 149KB - resprot_v7i10e11239_app2.pdf]

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Abbreviations

CTSA: Clinical Translational and Science Award
DMCI: Decision-Making Control Instrument
MUSC: Medical University of South Carolina

NASA: National Aeronautics and Space Administration
QuIC: Quality of Informed Consent
REDCap: Research Electronic Data Capture Platform
SAHL-E: Short Assessment of Health Literacy-English version
SUS: System Usability Scale
TLX: Task Load Assessment
UNC: University of North Carolina at Chapel

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Protocol

Using an mHealth App to Transition Care of Type 1 Diabetes from Parents to Teens: Protocol for a Pilot Study

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Abstract

Background: Type 1 diabetes mellitus (T1DM) afflicts approximately 154,000 people under the age of 20 in the United States. Most people with T1DM are diagnosed at a young age, and parents have to take on the responsibility of T1DM management. Eventually, the child must begin to transition to self-management. Adolescents often struggle to take on responsibility for all the necessary tasks to successfully self-manage their T1DM. In fact, approximately three-quarters of adolescents are not achieving American Diabetes Association–recommended glycated hemoglobin (HbA_{1c}) targets. This lack of adherence can lead to negative health outcomes.

Objective: The goals of this interdisciplinary proposal are as follows: (1) to develop a unique and theory-driven technology using a mobile phone app to promote self-management behaviors for adolescents aged 10-15 years with T1DM and their parents and (2) to explore the feasibility and impact of the self-management mobile app.

Methods: This study has two phases: app development and pilot testing. In the app development phase, the app will be conceptualized and a prototype will be tested. In Phase 2, the mobile app will undergo pilot testing to determine its feasibility and impact on diabetes self-management.

Results: The pilot test was launched in September 2017. Data collection for the final pilot test is underway, and results are forthcoming.

Conclusions: Adolescents with T1DM and their parents can have a difficult time managing the transition of diabetes care. It is hoped that this app can help. The focus groups and prototype testing have indicated promising outcomes of app use.

Trial Registration: ClinicalTrials.gov NCT03436628; https://clinicaltrials.gov/ct2/show/NCT03436628 (Archived by WebCite at http://www.webcitation.org/72tHXTE2Z)

International Registered Report Identifier (IRRID): RR1-10.2196/10803

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KEYWORDS

mHealth; adolescents; type 1 diabetes; mobile phone

Introduction

Type 1 diabetes mellitus (T1DM) afflicts approximately 154,000 people under the age of 20 in the United States [1-3]. Most people with T1DM are diagnosed at a young age, and parents take on most of the responsibility for T1DM management. Optimal treatment requires the entire family to quickly learn about the disease and to oversee its management [4]. Starting in the early teen years, the child must begin to transition to self-management. During this transition, adolescents often struggle to take on responsibility for all the necessary tasks in order to successfully manage their T1DM [2,5]. Approximately three-quarters of adolescents are not achieving American Diabetes Association (ADA)–recommended glycated hemoglobin (HbA_{1c}) targets. Achieving these targets requires consistent and dedicated management [6]. A lack of adherence to the prescribed treatment regimen can lead to negative health outcomes, such as the development of diabetic ketoacidosis, increased infections, and hospitalizations [7-9].

One reason for the lack of adherence is that as a child matures into an adolescent, communication between the child and his or her parent becomes increasingly difficult, and conflict often increases. There are data to suggest that improving communication between the adolescents and their parents facilitates a smoother transition to self-care and is one way to improve HbA_{1c} [10]. Mobile health (mHealth) technologies can also ease this transition by facilitating trust-building and improving family communication, relationships, and health outcomes. Nearly three-quarters of American teens (13-17 years old) have access to a smartphone [11]. Our hypothesis is that a mobile phone-based intervention that focuses on improving family communication will be effective in providing both the adolescents and their parents with real-time, tailored information about their diabetes and tools for communicating effectively.

Easing transition difficulties in an effort to increase positive health outcomes is imperative to the well-being of adolescents with T1DM and their families, and studies have shown that participants using mobile phone interventions had higher adherence rates and more participation than those that did not use the intervention [12]. Therefore, this study will develop a mobile app that addresses the difficulties of the adolescent transition to self-management and pilot test the app to determine its feasibility and impact on diabetes self-management. Below, we discuss the methodology for developing the app as well as the theoretical foundations guiding this development.

Methods

Study Design

This study has two phases that correspond with the study aims (Textbox 1): app development and pilot testing. In the app development phase, the app will be conceptualized and a prototype will be tested. In Phase 2, the mobile app will undergo pilot testing to determine its feasibility and impact on diabetes self-management. We did not utilize a control group because this is a feasibility study [13].

Theoretical Foundation

The social cognitive theory will inform the development of the intervention. The use of this theory to guide interventions has demonstrated success in changing behaviors around disease management [14-17]. The social cognitive theory posits that a change in an individual's environmental, personal, or behavioral factors will impact the other two factors [18-21]; thus, the relationship among these factors is reciprocal. The self-management mobile app is being developed to lead to changes in each of the three factors. For example, to change the adolescents' environmental factors, we will provide social support through a forum feature [22-24]. We believe that receiving messages from their parents via the self-management mobile app will also be a part of the environmental change [25-28]. Personal factors will be modified by prompts sent to the adolescents to set small and achievable daily goals, blood sugar reminders, and educational tips about living with T1DM to improve the adolescents' self-efficacy [29-34]. Behavioral change will result from reinforcement through reminders and awarding points for achieving goals and entering data. The points encourage use (behavior), which we predict will improve adolescent adherence [35]. As a result of all of these factors, children will have an improved HbA_{1c}, a higher quality of life, and reduced conflict with their parents, which we believe will reinforce the use of the self-management mobile app, strengthening the links. Figure 1 shows the theoretical model for the intervention.

Textbox 1. Specific aims.

Phase 1

Specific Aim 1: Develop a type 1 diabetes self-management mobile phone app intervention for parents and adolescents

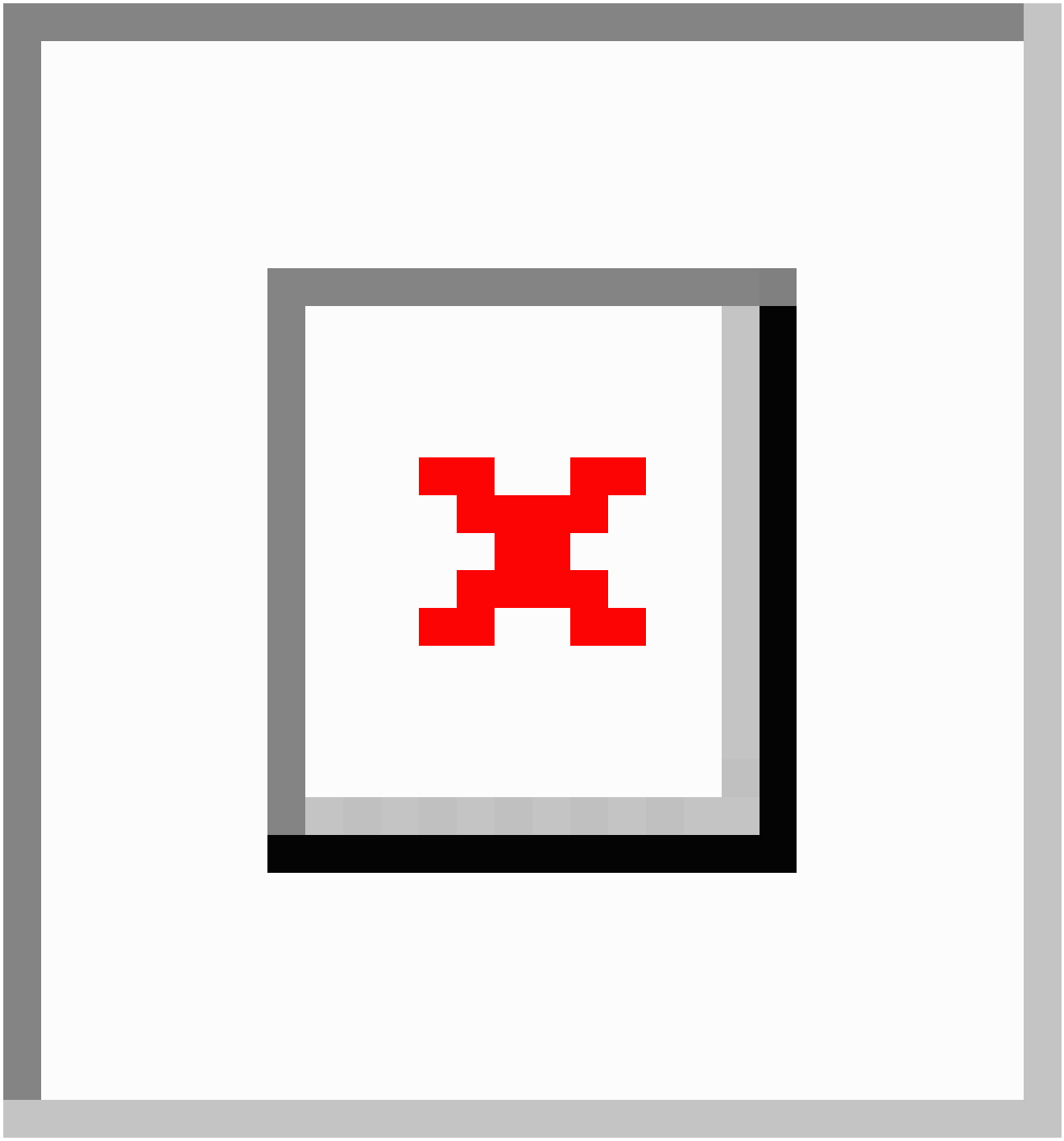
- Objective 1: Develop the self-management mobile app and finalize content
- Objective 2: Prototype testing

Phase 2

Specific Aim 2: Conduct pilot testing of the self-management mobile app to determine its feasibility and impact on diabetes self-management

- H1 (primary outcomes): Measures of app usage will be associated with increased adherence to self-management and lower glycosylated hemoglobin.
- H2 (secondary outcomes): Measures of app usage will be associated with increased quality of life, self-efficacy, and social support and decreased conflict between the adolescents and their parents.

Figure 1. Theoretical model. HbA_{1c}: glycated hemoglobin.



Phase 1: Technical App Development

The technical app development (Phase 1) will take place over a 9-month period. This process will be monitored through set goals, and progress will be measured by achieving two objectives of developing the self-management mobile app and finalizing content. To complete these objectives, content development will be completed based on several sources, including *Understanding Diabetes* [36] and other literature from the ADA, in conjunction with an expert panel who will also advise on the project during implementation. This panel includes a pediatric endocrinologist, a pediatric diabetes nurse practitioner, a college student with T1DM, and a parent of an adolescent with T1DM (not part of the study).

Based upon best practices in app design principles [37], we will also conduct focus groups with participants recruited from our target population. We will invite 6 adolescents and their parents for concept-testing focus groups. We will present the app concept and mock screenshots to the participants and solicit feedback with regard to the app's look and feel, message wording, and what would help the adolescents to log their values. The data from the focus groups will inform message content refinement, the timing of the messages, their appropriateness, and the ease of logging information. This information will inform the app's technical development. The technology development (app interfaces, Web portal, and servers) will be informed by the focus groups, concept testing,

and best practices literature. We have 10 benchmarks with deadlines for app development (Table 1).

Once the prototype is developed, the objective 2 will be met by prototype testing of the app. We will recruit 10 family dyads (each dyad includes a teen and his or her parent, n=20) to use the self-management mobile app prototype over a 4-week period. We will conduct usability interviews, measuring perceptions and satisfaction with the app. Additionally, server information will be used to quantify learning time, the efficiency of use, engagement, and user errors. All of the problems and issues identified in the usability interviews will inform app development and refinement.

The Mobile App

App Functionalities

The self-management mobile app will be an intervention mechanism to encourage adolescents aged 10 to 15 years to self-manage their diabetes by recording their values while allowing their parents seamless and unobtrusive access to the same blood glucose (BG) values, carbohydrate intake, and physical activity data, which will be time-stamped, encrypted, and sent to a remote server for storage.

Table 1. App development benchmarks.

Step	Time (in days)
Server management	13
User management	13
Server side logic	12
Data integration	13
Push logic	6
Versioning	12
Cache logic	6
Synchronization	8
Wireframe development	8
User interface design & development	33

The parent users will have a separate log-in and will be able to review their child's history of BG values, carbohydrate intake, and physical activity from their own phone to help their child make decisions about managing their diabetes. Parents may also send messages via the app to their child. However, the parent can still communicate outside of the app, and we will ask about this communication in the poststudy interviews.

Along with customizable test reminders and BG ranges, the app will also have an educational component and a moderated forum for the adolescents and the parents (separate forums) to post and discuss questions and comments to peers. The adolescents will be incentivized through the use of points accumulated based on usage. These points can be used by the adolescents to purchase accessories for a superhero avatar. As this is a feasibility study, we will have the adolescents manually input their BG readings into the app. While this may seem cumbersome, most meters and pumps do not have the ability to automatically send data through Bluetooth. Once we can determine the feasibility and other design requirements through this pilot, we will develop the app to be Bluetooth-enabled. The participants and their parents are responsible for notifying their medical providers regarding any issues with their diabetes. Our app will not cause an actual health concern, as it is just a monitoring and communication device.

Technical Details of the App.

The mobile app will be initially developed for the Android platform. Future iterations will include an iOS platform. Focusing on one operating system will allow us to develop a self-management mobile app using the highest-quality control standards. We have selected Android because it is the world's most popular platform [38]. Mobile phones will be provided to any participant who does not have a phone or one compatible with the app. The app will feature separate and secure log-in mechanisms for the adolescent user and parent user. All data will be stored on a remote encrypted server rather than the phone itself. If the phone is lost or stolen, we will have the ability to remotely erase the phone's contents and turn off the data plan associated with it. Technical specifications and functions of the app have been presented in Textboxes 2 and 3.

Phase 2: Intervention Study Methods

This portion of the intervention involves having the adolescents and their parents use the app over the course of 3 months.

Study Setting

Recruitment will take place in the Sparrow Hospital's Pediatric Subspecialty Clinic in Lansing, Michigan, United States. The Sparrow Endocrinology Clinic team consists of 1 registered pediatric dietitian, 1 full-time nurse practitioner, 2 certified diabetes educators, and 2 endocrinologists, all of whom provide diabetes care 4 days per week within the larger subspecialty clinic. All patients are scheduled to come to the clinic every 3 months for care.

Sample and Recruitment of Participants.

The clinic nurse diabetes educator will act as the site coordinator. Participants for the pilot testing will be recruited from the hospital's Pediatric Endocrinology Clinic. Invitations

will be mailed three times over 2 months to all of the potential participant dyads, as identified by hospital providers. Additionally, the health care providers in the clinics will be given a presentation on the study by the researchers so they can offer it to the families who meet the inclusion criteria during any typical interactions they have with the adolescent and parent.

Textbox 2. Technical specifications.

- Operating system: Android
- Data storage: Remote encrypted server
- Log-in mechanisms: Separate and secure log-in mechanisms for the adolescent user and parent user

Textbox 3. App functions. BG: blood glucose.

Child functions:

- Incentivized through the use of points accumulated based on usage
- Send messages via the app to their parent
- Customizable test reminders and BG ranges
- An educational component
- A moderated forum for the adolescents and the parents (separate forums) to post and discuss questions and comments to peers

Parent functions:

- Review their child's history of BG values, carbohydrate intake, and physical activity from their own phone
- Send messages via the app to their child
- Customizable test reminders and BG ranges
- An educational component
- A moderated forum for the adolescents and the parents (separate forums) to post and discuss questions and comments to peers

Textbox 4. Inclusion criteria.

Adolescents must:

- Have a type 1 diabetes mellitus (T1DM) diagnosis according to the American Diabetes Association practice guidelines [34]
- Be 10-15 years old
- Have had a diagnosis of T1DM for at least 6 months; have glycated hemoglobin>7 [35]
- Have had at least two outpatient visits in the past 2 years
- Be treated at the local clinic for diabetes
- Be fluent in English
- Have a parent or guardian willing to participate
- Be allowed to use a mobile phone for the study
- Have permission from their care team

Parents must:

- Have an adolescent with T1DM who is 10-15 years old
- Be fluent in English
- And have daily access to email and the internet (for appointment reminders and technical support)

Textbox 5. Exclusion criteria.

Adolescents:

- With a diagnosis of a major psychiatric or neurocognitive disorder (eg, traumatic brain injury, dementia, schizophrenia, bipolar disorder, borderline personality disorder, and intellectual disability)
- With significant medical conditions other than type 1 diabetes
- Being treated for thyroid disorders, celiac disease, or eating disorders
- In foster care

Parents:

- With a diagnosis of a major psychiatric or neurocognitive disorder (eg, traumatic brain injury, dementia, schizophrenia, bipolar disorder, borderline personality disorder, and intellectual disability)

If interested, the parent will contact the researchers to learn more about the study. A researcher will be in the waiting room of the pediatric endocrinologists, providing study information to possible participants. The researcher will explain the study and determine if the adolescent and parent are eligible through a brief screening questionnaire. We will recruit a total of 70 adolescent and parent dyads, which would correspond to similar past research studying T1DM and mobile phone interventions [12]. Inclusion and exclusion criteria have been presented in Textboxes 4 and 5, respectively.

Study Procedures.

During the study, there will be 4 contact points with the participants: the enrollment or baseline data collection visit (Visit 1), a midpoint review (Visit 2, 3 months after Visit 1), an end-of-study visit (Visit 3, 6 months after Visit 1), and a follow-up visit 3 months after app usage has stopped (Visit 4). Visit 1 (month 0) will be scheduled during the screening process. At Visit 1, a member of the research team will review and obtain informed consent (parent) and assent (adolescent) from the participants. The participants will then complete the baseline surveys to measure self-efficacy, quality of life, and social support and conflict; the laboratory will test the teens' HbA_{1c}, and we will download data from their glucometer or pump. If a participant does not have a mobile device that can download and operate the app, the research team will provide the participant with a device and data plan for the duration of the study. The researcher will demonstrate how to use the technology and have the participants use each of the functions. At Visit 2 (month 3), a research team member will test the adolescents' HbA_{1c} and download data from their glucometer or pump. The participants will also complete the survey at the midpoint. The midpoint data will be used to demonstrate whether any change at 6 months is part of an increasing trend, a plateau, or a waning trend. At Visit 3 (month 6), the participants will complete the survey and participate in interviews. Additionally, the adolescents' HbA_{1c} will be tested, and the meter or pump readings will be collected. Finally, any participant that has borrowed any equipment will need to return it at this time. Qualitative methods will also be used to better examine perceptions and intentions, whether participants were light users, or why participants dropped out of the study [39]. After Visit 3, the participants will not use the app for 3 months. At Visit 4 (month 9), all the participants will complete the survey. The researchers will test the adolescents' HbA_{1c} and download data from their glucometer or pump.

Outcome Measures

Specifically, the aim 2 seeks to determine the feasibility and impact on diabetes of the self-management mobile app among the adolescents and their parents. Demographic information will also be collected including current age, age at diagnosis, race, gender, parental status (ie, mom, dad, stepdad, etc), and method of diabetes treatment (eg, pump).

Hypothesis 1 seeks to demonstrate that adherence to self-management correlates with mobile app usage and a decrease in HbA_{1c}. HbA_{1c} data will be collected through the hospital laboratory system. The patient will be provided with a laboratory slip to obtain the baseline HbA_{1c} value. The patient will be instructed to obtain the lab results within 1 week. Once the results are obtained, they will be faxed to the principal investigator via a secure fax line. Adherence will be measured in two ways. First, the participants will complete the Diabetes Behavior Rating Scale [40]. Second, we will use data from the server to determine if they are monitoring blood sugar on schedule and what mechanisms of the app helped the adolescents follow the medical recommendations. For example, we will use time-stamped log-ins, number of sections the user visited, number of individual logs, communication through the app, educational information accessed, and duration of use per log-on.

Hypothesis 2 states that through use of the app, the participants' self-efficacy [29,41,42], quality of life [43-45], and perceptions of social support [46-48] will improve, and conflict [49] between the child and parent will be reduced from baseline to 3 months. These secondary outcomes are key in helping the adolescents maintain adherence and a normal HbA_{1c} [50-52] and will be measured through surveys. The survey instruments, the participants who will complete them, and reliability for each measure can be found in Table 2.

Analysis and Statistical Power

This is a feasibility study, so all analyses will be exploratory, focusing on identifying temporal trends in the self-management mobile app usage and changes in study outcomes and identifying associations between outcomes. Preceding the analyses, we will calculate summary statistics for all measures as well as

exploratory plots (histograms and box-plots) for all measures at each time point to identify outliers and potentially spurious values.

Trends over the 4 visits will be examined graphically as a function of time using nonparametrically smoothed plots to help identify when potential effects reach their maximum, plateau, and begin to decrease, which may indicate a time to target for additional interventions. At each time point, we will calculate pairwise correlations between the self-management mobile app usage measures and all study outcomes and examine bivariate scatter-plots with estimated trends for each pair. Distribution-appropriate correlations (Pearson or Spearman) will be calculated as appropriate for each measure and formally tested for statistical significance. These analyses will also be repeated using change from baseline as the outcome rather than the score itself, both as a simple bivariate analysis and using linear regression to model the change as a function of the app usage measures while controlling for baseline values. Analyses will also be repeated using paired *t* tests for differences in HbA_{1c} values from baseline to posttest to measure self-management adherence.

Statistical power will be established based on a small pilot study. A 2010 report on a small randomized controlled trial (RCT) of an mHealth intervention for T1DM in teenagers showed a significant change in self-management adherence from a mean of 3.7 (SD 0.4) at baseline to 3.9 (SD 0.4) at the 12-week follow-up, at an effect size of d=0.64 [53]. Given our longer follow-up period (6 months), we expect to observe a larger effect size in our feasibility study because HbA_{1c} has low variability in 3 months [54]. While using a small pilot study to calculate power may not be ideal, it provides a foundation for us to approximate this study's sample size in order to estimate the critical parameters necessary for this study [55]. The 2010 study also reported no change in HbA_{1c} for the intervention group, but there was an increase in the control group, with SDs ranging from 1.2 to 1.9. Considering that their groups were imbalanced with respect to HbA_{1c} at baseline, it is difficult to project a difference for our study except to note that observing no change in HbA_{1c} may be an improvement over a possible increase in adolescents with usual care. Despite our limited sample size, assuming the use of two-sided tests with a type 1 error rate of 0.05, with 70 participants we will have 80% power to detect relatively modest correlations of .29.

Table 2. Survey instruments.

Outcome	Measure	Reliability (α)	Participant
Adherence	Diabetes Behavior Rating Scale	.86	Child or parent
Glycated hemoglobin	Blood test—HbA_{1c}	N/A[a]	Child
Social support	Multidimensional Scale of Perceived Social Support	.81	Child or parent
Social support	Diabetes Family Behavior	.79	Child or parent
Self-efficacy	Diabetes Empowerment Scale-Short Form	.84	Child
Quality of life	Pediatric Quality of Life Inventory (general & diabetes specific)	.88	Child
Conflict	Diabetes Family Conflict Scale	.91	Child or parent

[a]N/A: not applicable.

In the event of unanticipated difficulties with recruitment or of attrition of up to 20%, leaving a final sample of 56, the correlation detectable with 80% power increases only slightly to .32. For *t* tests, N=70 provides 80% power to detect an effect size of 0.30, which is smaller than that reported in the RCT, while the effect size detectable with N=56 increases slightly to 0.34 [53].

Additionally, the primary foci of this study include assessment of the following: (1) the effect size of the intervention to power a larger study; (2) feasibility of the app; (3) practicality of data collection procedures; and (4) the ability to implement. We will also perform a post hoc analysis on personal characteristics and satisfaction related to use of the system. At the completion of the study (month 9), we will ask both those who completed the whole intervention and those who withdrew early about their experience with the intervention, including what worked well and what did not. Additionally, we will use the IBM computer usability satisfaction questionnaire to assess usability [56].

The interview data will be analyzed by developing broad code categories based upon perception themes and will serve as a preliminary sorting tool. The researchers will then use thematic analysis and create a list of common perceptions. Once a coding scheme is developed, two coders will perform a pretest by coding randomly selected interview transcripts in order to measure reliability. Coders will work together to reconcile any disagreements; this will allow us to achieve a high level of reliability.

Results

The study has been approved by the Institutional Review Board of Michigan State University, United States. We conducted focus groups prior to app development in April 2016 [57]. Prototype testing of the app was conducted in February 2017, and it included feedback regarding usability and satisfaction of the app [58]. The final pilot test was launched in September 2017. Data collection is underway, and results are forthcoming.

Discussion

Adolescents with T1DM and their parents often struggle during the transition from parent care to adolescent self-management [59,60]. This transition to young adulthood is challenging for

all families, but families facing the added complexity of diabetes management often find this time especially challenging. The proposed intervention is innovative as it aims to shift diabetes management responsibility to the adolescent and increase their independence while encouraging parents to remain engaged and supportive of their adolescent in an effort to ease some difficulties of this challenging time.

To do this, a mobile app for adolescents and their parents is proposed. Previous mHealth research indicates that mobile apps provide an innovative approach to impact health [12,61] using technology that is frequently part of adolescents' and parents' daily life [62,63]. However, very few existing apps have shown significant or sustainable improvements in adolescent self-management and overall health outcomes,[64] and none have directly involved the parents in the use of the app. In some apps that are currently available, the parents can receive the BG value, but they are not given any prompts on how to positively address blood sugar results and plan for care with their child. Our app will include communication through the app that may allow for adolescents to ask for help and communicate more honestly with their parent than they would in face-to-face communication [65]. This improved communication between adolescents and their parents has been shown to facilitate a smoother transition to self-care by improving communication between parents and adolescents, providing adolescents with tangible self-management skills, and providing families with social support and has been shown to improve HbA_{1c} [10,66,67].

One difficulty of using mobile app technology is keeping adolescents engaged with app use over long periods of time. This is also an issue when designing an intervention with outcomes that take 3 or more months to realize significant changes. Data suggests that the majority of user engagement begins to drop after 21 days of use [68,69]. To combat this difficulty, the app includes a points-based customizable avatar. However, it is important to note that researchers anticipate seeing a similar trend in engagement. Another difficulty seen in many studies is problems with recruitment and retention. To combat these difficulties, participants will be contacted frequently, flexible scheduling will be used for participant study meetings, and study newsletters will be sent to participants. In the event of unanticipated difficulties with recruitment or attrition, a final sample of 56 is acceptable [53].

After we have successfully completed this study, the data gathered will be integrated with machine learning in order to modify the app for a wider audience and better tailor the app to the individual user's behavior and usage preferences. Once completed, we will design and conduct a full-scale RCT. We will also expand the project to iOS (Apple phones). Additionally, we will seek to integrate the data into the patient's electronic health record.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the American Diabetes Association's Research Program.

[PDF File (Adobe PDF File), 509KB - resprot_v7i10e10803_app1.pdf]

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Abbreviations

ADA: American Diabetes Association
BG: blood glucose
HbA_{1c}: glycated hemoglobin
mHealth: mobile health
RCT: randomized controlled trial
T1DM: type 1 diabetes mellitus

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Protocol

Using Social Media and Web-Based Networking in Collaborative Research: Protocol for the Geriatric Medicine Research Collaborative

Geriatric Medicine Research Collaborative[1]

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Abstract

Background: Traditional pathways to promote research collaboration typically take years to expand beyond individual institutions. Social media and online networking provide an innovative approach to promote research collaboration.

Objective: The objective of this paper is to present the formation of the Geriatric Medicine Research Collaborative, United Kingdom — a national trainee-led research collaborative. This collaborative aims to facilitate research projects that will directly benefit older patients, improve research skills of geriatric medicine trainees, and facilitate recommendations for health care policy for older adults.

Methods: Our methods of collaboration comprised trainee-led meetings regionally and at national conferences, email communication, direct uploading of project material to our website, social media, and virtual meetings. Structured use of local, regional, and network leads has facilitated this collaboration. Having a clear virtual presence has been the key to the rapid development of the network.

Results: The use of social media and online networking encouraged the involvement of multiple regions early in the development of the collaborative and allowed rapid dissemination of project ideas. This facilitated the collection of large datasets and enhanced scientific validity of project outcomes. Furthermore, this has the potential to transform geriatric medicine research, as older patients have been historically excluded from large commercial trials due to multimorbidity, frailty, and cognitive impairment.

Conclusions: Perceived limitations to predominantly online or virtual collaboratives, including reduced accountability, and loss of interpersonal relationships are balanced by increased trainee engagement, high frequency of communication, and rapid access to a breadth of expertise. Utilization of virtual communication has the potential to lead to future interspecialty, interprofessional, and international collaboration, and to accelerate research that improves outcomes for older adults.

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KEYWORDS

collaborative; geriatrics; social media; virtual communication; trainee-led

Introduction

Background

Over the last 10 years, trainee-led research collaboratives have been established within the United Kingdom and internationally [1,2]. An example includes the general surgical research collaborative, which began regionally as the West Midlands Research Collaborative and has since led to the development of national and international surgical collaborations [3,4]. Traditional pathways to promote collaboration between researchers can take years to expand beyond individual institutions and regions. The traditional collaboration relied on networking events and meetings, which were limited to geographically accessible areas, chance meetings, or expensive trips. Social media and online networking provide an innovative

approach to the development and promotion of a research collaborative, with the potential to expand instantly and link otherwise unconnected individuals. We have utilized this approach in the formation of the "Geriatric Medicine Research Collaborative (GeMRC)" in the United Kingdom.

Collaboration has long been emphasized as an important aspect of academic development [5]. Traditional pathways of academic medicine have focused on the development of independent researchers [6,7]. While this may result in high-caliber researchers on an individual level, this approach may be detrimental to the academic progress overall; in grant development stages, independent researchers may be reluctant to share their niche of expertise with those outside of their organization for fear of affecting their own career progression [8]. In addition, due to the perceived skills and infrastructure required to undertake research with high patient benefit, such as a randomized controlled trial (RCT), individuals may be reluctant to undertake this early in their career. Furthermore, having a collaborative network ameliorates this trepidation.

Considering the aging population and disparate health and social care needs of older adults [9], the National Institute for Health Research (NIHR) recently released a themed call for research involving "Older adults with complex needs" [10]. Although geriatric medicine is a popular medical specialty, engagement with academic geriatric medicine has previously been less popular than other academic pathways [11]. There are a number of reasons for this finding. First, clinicians who typically choose a career in geriatric medicine tend to be more interested in direct patient care [12]. Second, there is a limited drive within the trainee curriculum to achieve research competence [13]. The majority of trainee time is spent in clinical areas, and, often, there are service requirements related to high rates of complex inpatients. In addition, the problem tends to cycle as trainers have limited experience of research to facilitate training of the next generation. Unfortunately, older adults have historically been excluded from research trials due to frailty, multimorbidity, and cognitive impairment [14], and results of trials undertaken in younger adults may not be generalizable [15,16]. Furthermore, engagement of geriatric medicine trainees in research may help increase translational research and, thus, lead to improvements in the care of this vulnerable population.

Aims and Objectives of Geriatric Medicine Research Collaborative

The following are the aims and objectives of GeMRC:

1. To enable the prompt conduct of research projects that are likely to have a direct impact on patient care upon completion.
2. To enable trainees in geriatric medicine to develop valuable research skills while undertaking their clinical training.
3. To obtain a clearer understanding of health care provision by conducting multisite audit and quality improvement projects to enable clearer recommendations for health care policy.

Methods

Development and Organization

GeMRC has been completely trainee-led from creation, through to project idea generation, and conduct of audit and research projects. Our initial dissemination involved creation of national [17] and regional websites [18], emphasizing the success of other research collaboratives. This approach encouraged the engagement of trainees, including those with minimal research experience. Our first meeting led to the generation of original ideas, which were subsequently presented to and discussed with other research collaboratives and the NIHR Clinical Research Network (CRN).

GeMRC rapidly expanded from a single region to a national collaborative involving 14 out of a potential 15 regions within the United Kingdom within 3 months of creation; the use of online dissemination of our collaborative was greatly beneficial toward this. GeMRC was advertised through trainee bulletins, discussion on general geriatric medicine websites [19], Twitter [20], and through contacting trainees directly via email to invite participation. This trainee-led grassroots approach encouraged early participation. Social media continues to be pivotal in encouraging engagement of trainees, other specialties, and nonmedical individuals. Additional social media networks including LinkedIn [21], Facebook [22], YouTube [23], and Periscope [24] have since been utilized. The use of general hashtags such as "geriatrics" and specific project-related hashtags such as "delirium" enables rapid dissemination to stakeholders.

Although Twitter has proven to be an efficient tool to engage with the academic community, additional social media networks have provided added benefits. The promotion of our collaborative and research projects using Facebook has encouraged engagement with trainees who have been previously less involved with academia; although Twitter has been commonly used within the academic community, usage beyond this has been limited by many trainees. Of note, Facebook has broadened our audience. LinkedIn has been beneficial in engaging with nonmedical individuals. We utilized YouTube to publish a PowerPoint presentation in relation to our most recent project, "Delirium Day Audit," discussed below. Similarly, Periscope is a social media outlet that offers live streaming; this was used to offer a live question and answer session prior to the audit.

One of the pivotal concepts of our research collaborative is that all members and researchers are considered equal. All publications will be published under the name of the GeMRC. All data collectors will be formally acknowledged as collaborators for authorship purposes for all of our studies. Specific trial and study steering groups will be listed separately to other collaborators as appropriate. Our approach to contribution is flexible, allowing trainees to be involved in the process of study design, obtaining ethical approval, public involvement, participant recruitment, analysis of results, and dissemination. Trainees may choose to be involved in all or part of these processes. However, in order to formalize

communication, we have developed a formal structure, described below.

Network Leads

The responsibility of the network leads is to oversee the GeMRC overall and to ensure regional communication and training of regional leads. This is currently the responsibility of the founding members. It is envisaged that over time, this role will rotate through trainees nationally. Network leads communicate with regional leads through a combination of email, WhatsApp, social media, and virtual meetings. WhatsApp has been especially useful in providing instant communication responses. Small virtual meetings were initially conducted with appear.in (free plan) [25]. The videoconferencing platform Zoom is now being used to enable larger meetings with all regional representatives [26]. These are conducted on weekday evenings on prearranged dates, at least four times each year; more frequent meetings may be organized in addition to these. The NIHR CRN Ageing group has recently developed two trainee representative roles. These trainees have formal involvement in GeMRC, along with the British Geriatrics Society (BGS) Research and Academic Development trainee representative; this has been invaluable in achieving support from the NIHR CRN Ageing group and the BGS, and senior academic geriatricians nationally.

Regional Leads

Regions within the United Kingdom have been divided according to the boundaries of regional training programs; this includes collaboration with the Welsh Geriatrician's Network [27]. This ensures ease of communication with trainees through regional trainee representatives for geriatric medicine training. The regional lead for GeMRC does not need to be the regional trainee representative, but he or she should maintain regular communication with the trainees to ensure that all trainees within the region are kept up to date about projects and GeMRC progress. In addition, the regional lead communicates with local leads about individual projects and arranges regional meetings as appropriate; this occurs through a combination of emails, website updates, and WhatsApp. Furthermore, regional leads are responsible for training local leads. Notably, the regional lead communicates with other regions as necessary through the network leads.

Local Leads

While we accept that not all trainees will wish to participate in all projects, we aim to have one local representative for GeMRC in each hospital trust. Local leads are responsible for the site conduct of all projects and local data collection. In addition, local leads are responsible for engaging consultants in our projects; working with local key stakeholders such as head of departments, specialist nurses, and allied health care professionals. Local leads also provide training to other trainees working locally. The local lead is required to communicate regularly with his or her regional lead through emails, website updates, WhatsApp, and virtual and in-person meetings.

Patient and Public Involvement

Individuals aged above 70 years are the fastest growing users of social media [28]. We intend to harness this by communicating our research on Twitter, LinkedIn, YouTube, and Periscope in terms understandable to nonmedical professionals. We have created a website specifically for the purpose of relaying the rationale, design, and findings of our research to nonmedically trained individuals [29]. Concurrently, we will use our national website and social media to facilitate the organization of regional discussion group meetings involving older adults and their carers.

Journal Club

Virtual journal clubs have recently grown in popularity. In contrast to traditional in-person journal clubs, virtual discussions enable those involved to read and critique papers in their own time and comment remotely. The most common method for conducting virtual journal clubs is to utilize social media. While this has the benefit of enabling a broad audience, comments and messages may be limited and the involvement may be time-dependent to prevent interspersion with comments pertaining to other topics. We have incorporated a membership function into our national website to enable the organization of a national journal club through a forum [30]. Files are uploaded directly to the forum. Members can review all files and comments in their own time and provide their own critique of journal papers. Although a national rota is created to participate in this, we have a flexible approach to involvement.

Results

Current Projects

The projects detailed below are all currently underway or in development. We plan to publish the protocol for our research projects in peer-reviewed journals so that these are widely available. The results of all of our projects will be presented at national conferences and published in peer-reviewed journals under the name of GeMRC.

Collaborative Research Projects

Ferric Carboxymaltose to Prevent Blood Product Use Following Operative Management of Neck of Femur Fractures

This RCT will assess the effect of ferric carboxymaltose on the postoperative prescription of packed red cells compared with standard care. In addition, secondary outcomes including the length of stay, mortality, and delirium incidence will be recorded. This trial will be supported by the Birmingham Clinical Trials Unit. We are currently in the process of applying for funding, initially through the NIHR Research for Patient Benefit funding program. The protocol for this trial will be published and widely available in the future.

Chlorhexidine Mouthwash to Prevent Hospital-Acquired Pneumonia in Older Hospital Inpatients

This RCT will assess the impact of chlorhexidine mouthwash on the incidence of hospital-acquired pneumonia. The protocol for this study is currently under development and will be published when finalized by our steering group. To ensure that this is a cost-effective study that can be conducted at scale, we will use a before- during- and after- intervention analysis.

Collaborative Audit and Service Evaluation Projects

Perioperative Management of Anaemia in Patients With Fractured Necks of Femurs

This project aimed to assess the current practice of perioperative management of anemia in patients undergoing operative management of the fractured necks of femurs across multiple hospital sites using retrospective electronic and paper notes assessment. Current management was assessed against agreed standards adapted from British Orthopaedic Society guidelines [31] and the National Institute for Health and Clinical Excellence blood transfusion guidelines [32]. This project was publicized through our website, emails, and Twitter. In addition, related documents were uploaded to our website for direct downloads. Seven sites participated in this initial study. Notably, results have been presented at the national BGS Spring Meeting 2018 and have assisted in providing preliminary data toward our proposal for the FErric carboxymaltose to preveNt blood proDuct use following Operative management of neck of Femur Fractures (FEND-OFF) study.

Evaluation of Current Practice of Mouth Care Amongst Older Medical Inpatients

This service evaluation aimed to assess the current standards of mouth care that older adults receive when admitted to hospital. Our methodology incorporated a 1-day flash evaluation of mouth care in hospitalized patients and a survey of relevant knowledge among UK doctors. We uploaded study-related documents to the website and disseminated the information via email. Our survey was hosted on Google Forms [33], and the link was disseminated via emails and Twitter. In the flash audit part of this study, 15 sites participated. We obtained 136 responses to our survey. Results have been presented at the National Spring BGS Meeting 2018 and will guide further multisite quality improvement projects and our proposal for the Chlorhexidine mOUthwash to preveNt hospiTal-acquired pnEumonia in oldeR hospital inpatients (COUNTER) study.

"Delirium Day Audit": Evaluation of Delirium Assessment and Recognition in Acutely Hospitalized Older Adults

This national audit was conducted on the World Delirium Day on Wednesday, March 14, 2018. Overall, 67 sites registered to participate in this audit, and results are currently being analyzed. In the United Kingdom, the National Institute for Health and Clinical Excellence guidelines recommend that all adults aged ≥65 years newly admitted to a hospital should be screened for delirium [34]. However, this is not always performed in practice; delirium remains underrecognized in many cases [35,36]. This study evaluated whether older patients had been assessed for delirium and whether delirium had been recognized. In addition, secondary data analysis was performed on the anonymized database to determine the point prevalence of delirium. We publicized our study through our website, WhatsApp, emails, Twitter, Facebook, and LinkedIn. Study-related documents were uploaded to our website, and a Google Docs spreadsheet was used to record participation at each site. Furthermore, a PowerPoint presentation to clarify the audit process was uploaded to YouTube, a live Web stream question and answer session was hosted on Periscope, and videos demonstrating delirium assessment using real patients were uploaded to a password-protected part of our website [37]. Local quality improvement projects are currently underway, and we will conduct a national reaudit later this year.

Funding

We have described the above processes for applying for research grants for specific projects. In the same way that all collaborators who contribute toward projects are acknowledged in authorship, we have agreed on a policy that all collaborators who contribute toward project development should be listed on grant applications. The initial set-up of GeMRC was free. We utilized our own skills in website development using the free Wix server and created our own logo using Paint 3D (Microsoft Corporation, United Kingdom), which has now become highly recognizable. Our logo has been incorporated into our Google, YouTube, Twitter, Facebook, LinkedIn, and Periscope accounts and also added to our email signature and WhatsApp group. In addition, we used free teleconference software as described. However, we anticipate that there will be ongoing costs related to the management of GeMRC. We have successfully obtained funding from a West Midlands BGS grant to cover regional and national networking costs. All West Midlands members were listed on our initial regional grant. This has been used initially to purchase the domain name for our website and remove Wix adverts. This has improved the credibility of our collaborative and improved the ease to locate it online. Further funding will be used for patient and public involvement activities.

Discussion

Trainee-led research collaboratives, driven by online networking and social media, are an innovative approach to conducting national audit and research projects. The use of social media and online networking allows rapid dissemination of project ideas and involvement of multiple regions early in the development of a collaborative. This facilitates the collection of much larger datasets and enhances the scientific validity of project outcomes. A particularly innovative approach has been to create a separate website specifically for the purpose of communicating our research ideas, project design, and results to nonmedically trained individuals.

Many older adults have complex needs. Conventional research may be less applicable to this group of patients; they are often underrecruited in studies or excluded because of their comorbidities [14]. Historically, there has been minimal emphasis on research within the geriatric medicine curriculum [13]. This can be considered both a positive and negative aspect. While the removal of coerce improves morale and enthusiasm of those undertaking research, the lack of organized structure and opportunities may reduce involvement in research. A lack of research infrastructure in geriatric medicine may have reduced the opportunity for involvement of trainees in research and subsequent retention in academic careers in geriatric medicine. GeMRC offers an opportunity to ensure rapid conduct of research projects from the generation of ideas to completion, with subsequent early implementation of changes into clinical practice to improve patient care.

There are limitations to a purely online research collaborative. Purely written electronic communication can lead to misinterpretation of concepts, less-developed interpersonal relationships, and reduced accountability. However, this is countered by the ease of communication and the ability to arrange virtual meetings at short notice, without expensive and time-consuming travel. In addition, email correspondence provides a clear written record of exactly when project timelines are planned and who is responsible for each stage. We believe online networking has the potential to change the way clinical geriatric research is conducted; this will benefit the trainees involved, improve patient outcomes, and shape the academic medicine of the future.

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Authors' Contributions

Carly Welch and Lauren McCluskey were the founding directors of GeMRC and contributed equally. Katy Madden, Natalie McNeela, Hannah Moorey, and Daisy V Wilson were involved in the initial set-up of GeMRC. Lynsey Ronan, Jane AH Masoli, Oliver Todd, Sarah J Richardson, Joanne K Taylor, Kumudhini Giridharan, Mary Ni Lochlainn, Emma Cunningham, Roisin Healy, Victoria Gaunt, Ruth H Willott, Kelli M Torsney, Stephen Makin, and Natalie J Cox are all regional representatives who have contributed toward national collaboration. Thomas A Jackson has provided consultant oversight.

Conflicts of Interest

None declared.

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Abbreviations

BGS: British Geriatrics Society
COUNTER: chlorhexidine mouthwash to prevent hospital-acquired pneumonia in older hospital inpatients
CRN: Clinical Research Network
FEND-OFF: ferric carboxymaltose to prevent blood product use following operative management of neck of femur fractures
GeMRC: Geriatric Medicine Research Collaborative
NIHR: National Institute for Health Research
RCT: randomized controlled trial

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Protocol

Design and Rationale of the National Tunisian Registry of Atrial Fibrillation: Protocol for a Prospective, Multicenter Trial

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Abstract

Background: Atrial fibrillation (AF) is an important health problem in Tunisia. A significant change in the epidemiological pattern of heart disease has been seen in the last 3 decades; however, no large prospective multicenter trial reflecting national data has been published so far. Robust data on the contemporary epidemiological profile and management of AF patients in Tunisia are limited.

Objective: The aim of this study is to analyze, follow, and evaluate patients with AF in a large multicenter nationwide trial.

Methods: A total of 1800 consecutive patients with AF by electrocardiogram, reflecting all populations of all geographical regions of Tunisia, will be included in the study, with the objective of describing the epidemiological pattern of AF. Patients will be officially enrolled in the National Tunisian Registry of Atrial Fibrillation (NATURE-AF) only if an electrocardiogram diagnosis (12-lead, 24-hour Holter, or other electrocardiographic documentation) confirming AF is made. The qualifying episode of AF should have occurred within the last year, and patients do not need to be in AF at the time of enrollment. Patients will be followed for 1 year. Incidence of stroke or transient ischemic attack, thromboembolic events, and cardiovascular death will be recorded as the primary end point, and hemorrhagic accidents, measurement of international normalized ratio, and time in therapeutic range will be recorded as secondary end points.

Results: Results will be available at the end of the study; the demographic profile and general risk profile of Tunisian AF patients, frequency of anticoagulation, frequency of effective treatment, and risks of thromboembolism and bleeding will be evaluated according to the current guidelines. Major adverse events will be determined. NATURE-AF will be the largest registry for North African AF patients.

Conclusions: This study would add data and provide a valuable opportunity for real-world clinical epidemiology in North African AF patients with insights into the uptake of contemporary AF management in this developing region.

Trial Registration: ClinicalTrials.gov NCT03085576; https://clinicaltrials.gov/ct2/show/NCT03085576 (Archived by WebCite at http://www.webcitation.org/6zN2DN2QX)

Registered Report Identifier: RR1-10.2196/8523

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KEYWORDS

atrial fibrillation; registry; North African; NATURE-AF

Introduction

Background

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and recent projections in Europe estimate that from 2010 to 2060, the number of adults aged 55 years and older with AF in the European Union will more than double [1]. With the aging population and associated prevalence of other cardiovascular diseases, the burden of AF is projected to increase. It is estimated that by 2050, the prevalence of AF in Africa will be greater than in any other region of the world [2]. Given the increasing prevalence and AF's association with significant morbidities and mortality, this increase would have major public health implications.

In the last decades, a significant change in the epidemiologic and etiologic patterns of cardiovascular diseases has been seen in North Africa with a decrease in rheumatic heart disease and increase in hypertensive and ischemic heart disease [2,3]. The World Health Organization reported trends in the incidence and prevalence of acute rheumatic fever and rheumatic heart disease for each continent based on literature from 100 countries around the world between 1970 and 2009 [4,5]. However, data from Africa are scarce and do not capture the entire time frame. As for all heart diseases, there are insufficient contemporary population-based data describing the epidemiologic pattern of AF in North Africa and especially in Tunisia. In 2003, valvular AF secondary to rheumatic heart disease was the most common etiologic form of AF [6].

Numerous registries and surveys have been described in different European, Asian, and American countries—Euro Observational Research Programme–Atrial Fibrillation pilot general registry [7], Japanese Rhythm Registry [8], Global Anticoagulant Registry in the Field [9], Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation [10], the nationwide US Practice Innovation and Clinical Excellence Registry [11], Outcomes Registry for Better Informed Treatment of Atrial Fibrillation [12], and Chinese Atrial Fibrillation Registry study [13]. However, few data on the demographic characteristics, outcome of AF patients, and quality of anticoagulation control achieved in AF patients receiving routine medical care are available in North Africa and especially in Tunisia.

Demographic and prognostic AF data from other ethnic groups would not be generalizable to our population. Thus, a register

or a survey dealing with the demographic and prognostic characteristics of AF in Tunisia is essential, making it possible to identify its specific characteristics inherent in part to ethnic particularities but especially to particularities of the local health system.

Registry Objectives

The National Tunisian Registry of Atrial Fibrillation (NATURE-AF) is a prospective observational accumulation of data used in the investigation of the optimal intensity of anticoagulation in Tunisian AF patients and present status of anticoagulation treatment in Tunisia.

The primary end point of NATURE-AF is to describe the incidence of stroke or transient ischemic attack (TIA), thromboembolic event, and cardiovascular death every 3 months up to 1 year.

The secondary end points are as follows:

- Hemorrhagic accidents, every 3 months up to 1 year
- International normalized ratio (INR) every month for 1 year
- Mean time in therapeutic range (TTR) obtained in patients who receive anticoagulant therapy

Methods

Study Design and Patient Enrollment

NATURE-AF is a prospective, observational registry with a 1-year follow-up period. The enrollment occured all over Tunisia between March 1, 2017, and May 31, 2017. The registry population comprised consecutive in- and outpatients with AF presenting to cardiologists. Consecutive patients were screened for eligibility at the time of their presentation to a cardiologist (hospital or medical center). All patients provided written informed consent. Patients were officially enrolled in NATURE-AF only if they were aged 20 years and older and had had at least 1episode of AF recorded on a standard 12-lead electrocardiogram or on 24-hour Holter monitor. The qualifying episode of AF should have occurred within the last year and could be valvular or nonvalvular AF. Valvular AF is AF in patients with mitral stenosis or prosthetic heart valves. Patients did not need to be in AF at the time of enrollment. All patients admitted for catheter ablation, initiation of drug therapy, or cardioversion (electrical or pharmacological) were eligible to be included.

Exclusion criteria were AF due to reversible causes (eg, thyroid disease and pulmonary embolism) including postoperative AF (≤3 months), life expectancy less than 12 months, acute coronary syndrome, isolated atrial flutter, mental disorders, and ongoing anticoagulation for reasons other than AF.

Sample Size and Data Collection

A minimum of 10 consecutive patients per cardiologist were enrolled with a target of 1800 patients for NATURE-AF. A total of 186 cardiologists agreed to participate.

While it was anticipated that most investigators would be hospital-based cardiologists, recruitment by office-based cardiologists was allowed if follow-up of patients was deemed feasible.

The plan was to have 1 baseline visit and 1 visit every 3 months over a 1-year period. Enrollment into the registry started March 1, 2017, with an inclusion period estimated up to 3 months. All patients were followed for 12 months. During this period, all participants revisited their cardiologists at the usual intervals (3 months), and patients taking oral anticoagulant therapy consult (or visited) at least once every month for INR to be measured.

The data collected were managed by the Clinical Suite platform (Dacima Software), which complies with international standards including US Food and Drug Administration 21 Code of Federal Regulations Part 11, US Health Insurance Portability and Accountability Act, International Conference on Harmonisation, and Medical Dictionary for Regulatory Activities. The Clinical Suite platform allowed us to track the data entered, check for inconsistencies and missing data, and schedule monitoring visits. A steering committee was set up to monitor patient inclusions, verify data sources, perform the audit trail, and prepare the statistical analysis plan for the study. Data were collected every 3 months regardless of patient clinic follow-up. All incident events and therapeutic changes were entered at each collection interval.

Baseline data included patient demographics, medical history, cardiovascular history, details of AF history and therapies, vital signs, laboratory measurements, electrocardiographic data, cardiac imaging parameters, details of medical management, and any contraindications to anticoagulation. At follow-up, major incident events and procedures, subsequent vital signs, laboratory studies, imaging parameters, and medication changes were recorded, and the daily acenocoumarol (Sintrom) dose and INR value were noted for all patients taking acenocoumarol. In-depth data regarding antithrombotic therapies, dosing, discontinuations, and reasons for discontinuations were included in follow-up medication data.

Timeline

Patient enrollment and data collection began in March 2017 and continued until the end of May 2017. Follow-up continued until all patients had 1-year data. Figure 1 describes the study protocol.

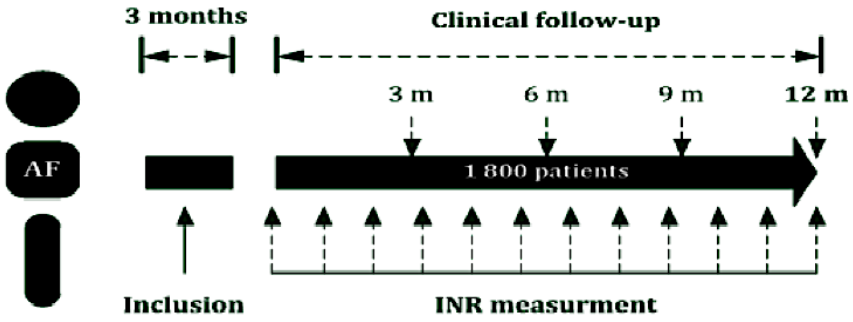
Outcomes

During follow-up, the end points of this observational study were symptomatic stroke including TIA, systemic thromboembolism, myocardial infarction, incident heart failure, cause-specific hospitalization, major bleeding, and all causes of death.

Major bleeding is defined by the International Society of Thrombosis and Hemostasis criteria; this includes bleeding events meeting at least one of the following criteria [14]:

- Decrease in hemoglobin ≥2 g/dL
- Transfusion of ≥2 units of packed red blood cells or whole blood
- Any bleeding in a critical site (intracranial, intraspinal, intraocular, intra-articular, pericardial, retroperitoneal, or intramuscular with compartment syndrome)
- Any fatal bleeding

Figure 1. Study protocol AF: atrial fibrillation; INR: international normalized ratio.



Additional unique, detailed data on management of bleeding events were collected and included the use of any blood products or transfusions, potential reversal agents, and necessity for invasive management of bleeding events. Any patient in whom a primary end point was encountered was evaluated by computed tomography or magnetic resonance imaging for precise diagnosis and required an INR value on the closest possible day to their revisit day to their cardiologist.

INR will be recorded monthly and TTR will be calculated according to Roosendaal's algorithm with linear interpolation [15].

Ethical Considerations

Ethics approval was obtained from the Human Research Ethics Committees at Abderrahmen Mami Hospital in Tunis. Ethics review boards in each participating hospital approved their participation. Informed consent from individual patients was obtained before participation in long-term follow-up. The study was performed according to the ethical principles for medical research involving human subjects specified in the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practices.

Statistical Analysis

Continuous variables will be described by mean and standard deviation or as median and interquartile range. Categorical variables will be described by the size and frequency of every modality. Means comparison will be performed by analysis of variance or by nonparametric tests if the hypothesis of normality is rejected. The normality of continuous variables will be verified with the Shapiro-Wilk test. The statistical tests are bilateral with a 95% confidence interval.

A chi-square test will be performed for categorical variables. Yates correction or the Fisher exact test will be used if the conditions of validity for the chi-square test are not met.

A multivariate analysis will be performed with anticoagulant treatment (over or undertreated) as dependant factor. The independent variables will be age, gender, body mass index, type of AF, combined therapy. Univariate logistic regression will be carried out with a 10% output threshold. The final model will be performed with the parameters selected by the backward stepwise method of Wald. The selected variables in the final model will be tested at the 5% threshold. The interaction between selected parameters is tested at the 10% threshold.

The TTR will be calculated by the method first described by Rosendaal et al [8], which uses linear interpolation of INR values in each patient under oral anticoagulant treatment to calculate the percentage of days when the INR is in the therapeutic range (2.0-3.0) for nonvalvular AF.

Expected Implications

The NATURE-AF is the first large-scale investigation to clarify the contemporary demographic data, management and outcomes of AF patients, and frequency and quality of oral anticoagulation in Tunisian AF patients.

Oversight and Leadership

The protocol of NATURE-AF was approved by the Tunisian Society of Cardiology and Cardiovascular Surgery. The NATURE-AF study was submitted to ClinicalTrials.gov [NCT03085576].

Study Sponsorship

NATURE-AF is sponsored by the Tunisian Society of Cardiology and Cardiovascular Surgery.

Results

About 95 cardiologists included 918 patients in the registry with a 1-year follow-up period. All patients provided written informed consent. Patients were officially enrolled in NATURE-AF only if they were aged 20 years and older and had had at least 1 episode of AF recorded on a standard 12-lead electrocardiogram or on 24-hour Holter monitor.

Discussion

Summary

Numerous registries and surveys have been described in different European, Asian, and American countries [7-13,16-19], but few contemporary data on the demographic characteristics, outcome of AF patients, and quality of anticoagulation control achieved in AF patients receiving routine medical care are available in North Africa and especially in Tunisia.

Only 2 published studies have described the epidemiological data on Tunisia [5,15,16]. In 2003, Drissaet al [6] described a multicentric study with 1134 patients presenting with a first episode of AF between January 1985 and December 2000. The average age was 58.6 (SD 15-60) years; 57.8% (656/1134) were

male and 42.2% (478/1134) were female. The most common etiology of AF identified was rheumatic carditis (36.1%). AF was idiopathic in 27.7% of cases. Higher morbidity and mortality were demonstrated in AF patients with a 5-year survival of 85%.

Recently, geographic differences have been highlighted by Gamra et al [16,17]. The RealiseAF international cross-sectional survey enrolled 10,523 patients (with at least 1 documented AF episode in the preceding 12 months) from 831 sites; 26 countries from 4 continents participated in the study with Middle East and North Africa participation from Algeria (n=310), Egypt (n=458), Lebanon (n=191), Morocco (n=250), and Tunisia (n=471). AF patients from the Middle East and Africa were significantly younger and more frequently female compared with those originating from the rest of the world. A $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke) score ≥2 was observed in 64.2% of the patients originating from Europe versus 58.3%, 57.8%, and 43.6% from Latin America, Asia, and the Middle East and Africa, respectively. Among those patients with a $CHADS_2$ score ≥2, there were also important geographical differences with respect to the use of antithrombotics: the proportion of patients not receiving any antithrombotic therapy ranged from 11.4% in the Middle East and Africa to 27.6% in Latin America. Conversely, the use of oral anticoagulants was highest in the Middle East and Africa (66.7%) and lowest in Asia (31.7%) [16,17].

Despite the many complexities associated with the use of vitamin K antagonists (VKA), it remains a mainstay of anticoagulation therapy. Acenocoumarol, a derivative of coumarin, is the most popular VKA used in Tunisia and numerous countries around the world. Maintaining therapeutic range in patients treated with VKAs has always been challenging, and the potential consequences of deviating from the therapeutic range are deleterious.

Although not easily achieved, high anticoagulation control, expressed as TTR, has a paramount effect on patient outcomes, reducing stroke events and mortality rates.

This large, contemporary longitudinal study of Tunisian AF patients will provide a unique opportunity to answer many clinical questions. The NATURE-AF study is important in several respects. First, systematic observational and outcomes data can be generated from this registry study, which is especially valuable given that evidence for Tunisian AF patients is limited. Second, treatment of AF is changing dramatically, and AF management needs to be evaluated in real-world studies. Third, the NATURE-AF study provides a good opportunity to compare treatment and response variation among AF populations in Africa for comparison with different countries and evaluate adherence to recent guidelines.

Conclusions

NATURE-AF will fill a significant gap in the dynamic landscape of AF care and research. It will provide unique and necessary data on the management and outcomes of AF patients treated. This study will yield the largest contemporary longitudinal cohort of patients with AF in Tunisia and would provide a valuable opportunity for real-world clinical epidemiology with insights into the uptake and outcomes of contemporary AF management.

Conflicts of Interest

None declared.

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Abbreviations

AF: atrial fibrillation
CHADS$_2$: congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke
INR: international normalized ratio
NATURE-AF: National Tunisian Registry of Atrial Fibrillation
TIA: transient ischemic attack
TTR: time in therapeutic range
VKA: vitamin K antagonist

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Protocol

Performance, Acceptability, and Usability of Respiratory Rate Timers and Pulse Oximeters When Used by Frontline Health Workers to Detect Symptoms of Pneumonia in Sub-Saharan Africa and Southeast Asia: Protocol for a Two-Phase, Multisite, Mixed-Methods Trial

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Abstract

Background: Pneumonia is one of the leading causes of death in children aged under 5 years in both sub-Saharan Africa and Southeast Asia. The current diagnostic criterion for pneumonia is based on the increased respiratory rate (RR) in children with cough or difficulty breathing. Low oxygen saturation, measured using pulse oximeters, is indicative of severe pneumonia. Health workers often find it difficult to accurately count the number of breaths, and the current RR counting devices are often difficult to use or unavailable. Nonetheless, improved counting devices and low-cost pulse oximeters are now available on the market.

Objective: The objective of our study was to identify the most accurate, usable, and acceptable devices for the diagnosis of pneumonia symptoms by community health workers and first-level health facility workers or frontline health workers in resource-poor settings.

Methods: This was a multicenter, prospective, two-stage, observational study to assess the performance and usability or acceptability of 9 potential diagnostic devices when used to detect symptoms of pneumonia in the hands of frontline health workers. Notably, 188 possible devices were ranked and scored, tested for suitability in a laboratory, and 5 pulse oximeters and 4 RR timers were evaluated for usability and performance by frontline health workers in hospital, health facility, and community settings. The performance was evaluated against 2 references over 3 months in Cambodia, Ethiopia, South Sudan, and Uganda.

Furthermore, acceptability and usability was subsequently evaluated using both qualitative and quantitative methodologies in routine practice, over 3 months, in the 4 countries.

Results: This project was funded in 2014, and data collection has been completed. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018.

Conclusions: This is the first large-scale evaluation of tools to detect symptoms of pneumonia at the community level. In addition, selecting an appropriate reference standard against which the devices were measured was challenging given the lack of existing standards and differences of opinions among experts. The findings from this study will help create a standardized and validated protocol for future studies and support further comparative testing of diagnostic devices in these settings.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12615000348550; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367306&isReview=true (Archived by Website at http://www.webcitation.org/72OcvgBcf)

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KEYWORDS

childhood pneumonia; diagnostic tools; low-income country; pulse oximeter; research design; respiratory rate counting

Introduction

Background

Pneumonia is one of the leading causes of death in children aged under 5 years, accounting for an annual 944,000 deaths globally, and 60% of these deaths occur in just 10 countries in South Asia and sub-Saharan Africa [1]. Deaths from pneumonia in children result mostly from delayed presentation to appropriate care, inappropriate treatment, or presuming the symptoms are of malaria [1]. Children with severe pneumonia have additional symptoms and danger signs such as chest in-drawing, stridor, and wheezing, which some health care workers are not able to adequately recognize, and subsequently, such children are treated with or referred for antibiotic treatment and oxygen therapy [2].

To diagnose pneumonia, frontline health workers are taught to observe a child's chest for a full minute to visually identify and count the child's breaths or respiratory rate (RR) and assess whether the RR is higher than the normal parameters for a child of that age, as defined by the World Health Organization (WHO) [3]. Counting the RR can be challenging in itself for health workers, and the misclassification of observed rate is common.

However, even with the deployment of the 1-minute acute respiratory infection timer in the early 1990s, counting the RR continues to prove challenging, as children breathe irregularly and faster than adults and may not sit still for a full minute. Misclassification of the observed rate is, therefore, still common, leading to incorrect diagnosis and, consequently, inappropriate treatment [4-7].

In addition, the acute respiratory infection timer has several shortcomings, such as short battery life and a distracting ticking sound every second, which can lead a health worker to count the sound instead of the chest movements. In a recent observational study, only 3 of 10 Mozambican community health workers (CHWs) counted the RR in children with a cough; of them, 1 counted the ticking of the timer, resulting in an RR of 60 breaths per minute, whereas other CHWs carried the timer but never used it, and the timer did not work in one case [8].

In addition, delays in seeking treatment put children at risk of developing severe pneumonia, and the inability of health care workers to adequately recognize danger signs and urgently refer children to a higher level of care leads to the death of many children. Hypoxemia, a symptom of severe pneumonia, has been identified as a predictor for morbidity and mortality in children with respiratory illness [9]. However, hypoxemia is poorly identified on the basis of clinical findings alone [10]. While pulse oximetry can be used to measure oxygen saturation (SpO_2) and is a reliable and noninvasive method for identifying children with hypoxemia, pulse oximeters are rarely available outside of higher-level facilities in resource-constrained countries.

Integrated community case management (iCCM) is an approach developed by the WHO, United Nations Children's Fund (UNICEF), and partners [11] where CHWs are trained to identify and treat pneumonia, malaria, diarrhea, and malnutrition in children aged under 5 years, as well as refer severely ill children to the nearest health facility. Evidence in African countries shows that health workers, if properly trained and equipped, can potentially reduce child deaths from malaria, pneumonia, and diarrhea by up to 60% through the delivery of iCCM [12]. The integrated management of childhood illness (IMCI) was developed by the WHO to support health workers in health centers to better manage childhood illnesses [13].

More recently, and partly as a response to the scale-up of large iCCM projects in sub-Saharan Africa and Southeast Asia, new pneumonia diagnostic aids have been developed by industry, academia, and other partners to improve the accuracy and effectiveness of diagnosing pneumonia in resource-poor contexts [14].

Study Aim and Objectives

This paper presents the protocol of a study aimed to identify the most accurate, acceptable, scalable, and user-friendly RR counters and pulse oximeters for the diagnosis of pneumonia symptoms in children by CHWs and first-level health facility

workers (FLHFWs) with different levels of training in 4 countries: Cambodia, Ethiopia, South Sudan, and Uganda. The two main objectives were (1) to evaluate the accuracy of 9 RR counters and pulse oximeters in the hands of CHWs and FLHFWs in 4 low-resource countries and (2) to assess the usability and acceptability of the 9 devices among CHWs and FLHFWs in 4 low-resource countries when used in the routine practice over a 3-month period.

Methods

Ethical Approval and Consent to Participate

The study was approved by the ethical review boards in each study country at the national or regional level: in Ethiopia, from the Southern Nations Nationalities Peoples' Region Health Bureau Health Research Review Committee (Ref: 6-19/10342); in Uganda, from the Uganda National Council for Science and Technology (Ref: HS 1585); in South Sudan, from the Research and Ethics Committee at the Government of South Sudan, Ministry of Health (dated May 23, 2014); in Cambodia, from the National Ethics Committee for Health Research (Ref: 0146 NECHR); and by the Regional Ethics Committee in Stockholm, Sweden (Ref. 2017/4:10). Participants were recruited only after obtaining written informed consent. The clinical evaluation is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12615000348550).

Study Design

A two-phase, mixed-methods design was developed to examine the performance, acceptability, and usability of the 9 devices in the 4 countries (Figure 1). The conceptual framework for the design was adapted from the WHO documents "Health technology assessment of medical devices" [15] and "Introducing new technology safely" [16].

The first phase, the performance evaluation element of the study, was a multicenter, single-blind comparison of the performance of devices to detect symptoms of pneumonia in the hands of frontline health workers using 2 reference standards. The second phase, the acceptability and usability evaluation element of the study, was a mixed-methods, multicenter, observational study using both qualitative and quantitative data to compare the acceptability and usability of devices to detect symptoms of pneumonia in the hands of CHWs and FLHFWs in routine practice.

Study Sites

This was a multicountry study implemented in Cambodia, Ethiopia, South Sudan, and Uganda as all 4 countries have a high proportion of deaths of children under 5 years caused by pneumonia (16%-21%), as well as a high incidence of pneumonia, and all have implemented the Ministry of Health-defined iCCM and IMCI programs. However, the characteristics of the health worker programs, such as the length of training, literacy level, and RR timing devices used, differed by country (Table 1).

The study sites selected for conducting phase 1 were all district hospital-level facilities selected after the analysis was conducted on patient flow to understand whether the individual research sites could support the sample size required by the study for enrollment, as it would not have been possible to achieve the sample if phase 1 had been conducted at the community level (Table 2).

Phase 1 research sites were as follows: Mpigi General Hospital, approximately 45 miles from Kampala in Uganda; Yrgalem District Hospital in Southern Nations and Nationalities and People's Region in Ethiopia; Borkeo District Hospital in Ratanakiri province in Cambodia; and Aweil General Hospital in Northern Bahr el Ghazal state in South Sudan. For phase 2 of the study, frontline health workers were selected depending on having participated in phase 1 and being within 20 km of the health facility used in phase 1 in order to have access to the functioning oxygen equipment and severe illness case management capabilities.

Figure 1. Stages of introducing a new technology.

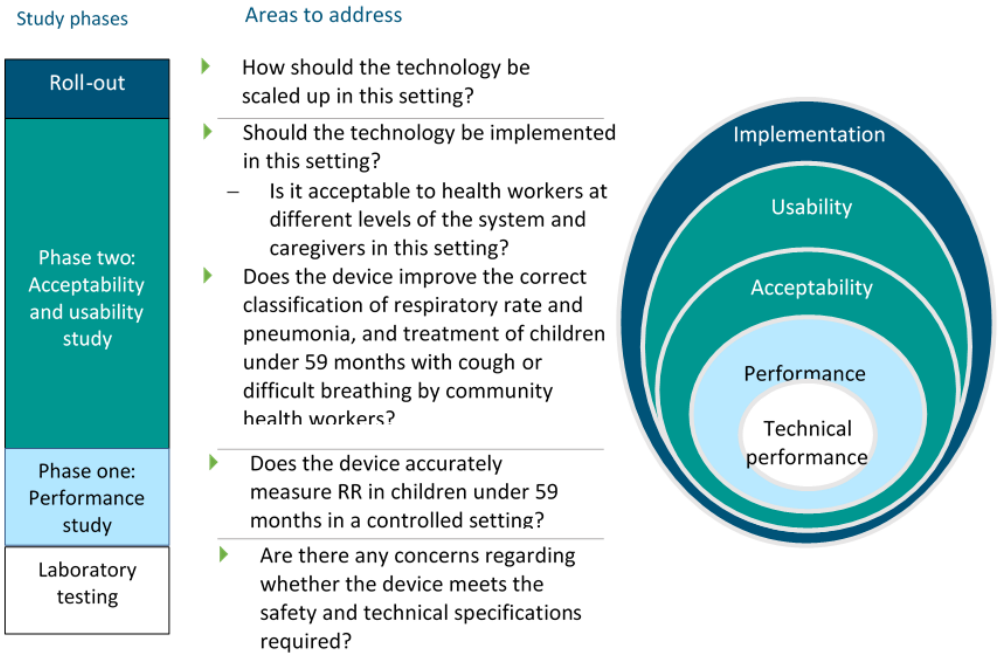

Table 1. Country implementation of pneumonia diagnosis and treatment at community level.

Characteristics	Cambodia	Ethiopia	South Sudan	Uganda
Pneumonia deaths (% of total under-5 deaths) [17]	17	17	21	16
Pneumonia incidence in children under 5 years (number of episodes per child per year) [18]	0.25	0.28	0.32[a]	0.27
Proportion of children aged under 5 years with suspected pneumonia and receiving antibiotics (%) [19]	39	7	33	47
Name for community health worker (CHW)	Extended village malaria worker	Health extension worker	Community drug distributor	Village health team member
Length of initial training	5 days (2 days malaria training + 3 days in sick child case management)	1 year	6 days	11 days (5 days basic training + 6 days in sick child case management)
Literacy level	Low	High	Extremely low	Low-median
Pneumonia diagnosis tool	Acute respiratory infection (ARI) timer	Wrist watch or ARI timer	ARI timer + beads	ARI timer
Catchment population per CHW	130-150 households	400-500 households	250-300 households	250-500 households
Average caseload per month	8	12	9	12

[a]Data are for Sudan.

Table 2. Demographic characteristics of the study sites in Cambodia, Ethiopia, South Sudan, and Uganda.

Description	Cambodia Ratanakiri province	Ethiopia (Dale & Shebedino Districts), SNNPR[a]	South Sudan (Aweil West & Center counties) Northern Bahr el Ghazal State	Uganda, Mpigi District
Population	184,000	529,041	128,295	250,548
Children under 5 years population, N (%)	37,720 (20.50)	82,582 (15.61)	25,000 (19.49)	51,363 (20.50)
Number of community health workers	270	161	1683	650
Number of health centers	23	19	20	39
Number of hospitals	2	2	1	1

[a]SNNPR: Southern Nations and Nationalities and People's Region.

Device Selection

A number of activities were conducted before the field trials to select the test devices. First, the formative research was conducted to inform the attributes used in the subsequent device scoring [20]. Second, an initial landscape review was conducted where 188 possible devices were identified [21]; these devices were further evaluated in a review of technical specifications [22]. Third, all potential devices were scored and ranked using 20 device attributes, including measures of usability, utility, scalability, and user acceptance. Multimedia Appendix 1 provides the table with the device scoring based on the attributes. In contrast to the respiratory timing devices identified, the 8 selected pulse oximeters had not previously been field-tested, and before taking them to the field trials, they were first tested in a laboratory for accuracy and environmental robustness. Based on the laboratory test results, the final 9 devices were taken forward to the performance evaluation phase (Multimedia Appendix 2), that is, 4 RR devices (manual and assisted counters) and 5 pulse oximeters (fingertip and handheld devices) [23].

The devices allocated to each country were based on the suitability for individual country context; overall, 9 devices were tested for performance (phase one) and the usability and acceptability in the routine practice (phase 2).

Sample Size

The sample size calculation for phase 1 was based on the precision of the mean difference between the device and the reference respiratory count, assuming the normal distribution. An SD of 7 for the difference was obtained in a previous study evaluating the performance of RR counters [24] and in requiring a maximal total length of the 95% CI of 4 units, which is the same range as the WHO-accepted maximal absolute breathing rate deviance (eg, ±2 breaths per min); the minimum sample size was 47 children per strata for independent observations. The two age strata in the study were (1) 0-60 days and (2) 2-59 months, and 3 device pairs per country gave a total sample size of 282 children. The sample size was then increased by 50% to 423 and rounded off to 430 children per country to accommodate for potential clustering at the CHW level [25]. For the usability and acceptability of the routine practice assessment, a sample of 20 CHWs and 5 FLHFWs was recruited to do the assessments in each country over the 3 months.

Outcomes

The primary outcome for phase 1 was the agreement between each health worker measurement, using the test device, and that of the reference standard, calculated as the proportion of 1-minute observations that were within ±2 breaths or ±2% SpO_2 for each of the 9 devices. The secondary outcomes included the agreement in classification of the breath rate into (1) normal or fast breathing and oxygen saturation into (2) normal oxygen saturation (SpO_2≥90%) or hypoxemia (SpO_2<90%) and included agreement statistics appropriate for situations when no gold standard exists, such as positive percent agreement, negative percent agreement, and Cohen kappa statistic.

The primary outcome for phase 2 (the usability and acceptability evaluation) was acceptability, based on users' perceptions of the different devices used. Secondary outcomes for phase 2 included the proportion of users who accurately followed the correct procedures and the caregivers' perceptions of, interaction with, and reaction to the devices when used on children.

Study Procedures

In phase 1, all children aged 0-5 years presenting at the health facilities where the study was conducted were screened for eligibility and invited to participate. All young infants aged 0-60 days were eligible, as were children aged 2-59 months with a cough and/or difficulty in breathing. Children with an illness of >2-week duration or exhibiting one or more of the IMCI danger signs (severe dehydration, agitation, inconsolable, neck stiffness, active convulsions or fits, unconscious or lethargic, not breastfeeding, and vomiting everything) as well as those with severe burns, with neutropenia, with a severe infectious disease, or ineligible as advised by the supervising clinician were excluded.

In the absence of a gold standard, 2 reference standards were used for phase 1 of this study: (1) an IMCI-trained expert clinician (EC) and whose RR counting skills were standardized to ±2 breaths per minute on 5 video recorded children and (2) an automated monitoring device (Masimo Root patient monitoring and connectivity platform with Phasein ISA CO_2 capnography using nasal cannulas and Radical 7 pulse oximeter) [26] that provided a measurement for the same period. All health workers received 2 days of training prior to data collection, including a refresher module on iCCM as well as practice sessions on RR counting and using a new device. All health workers needed to receive a pass mark of ≥90% on a

competency-based assessment before participating in data collection. On consenting to the studying and entering the research room, a child was positioned comfortably on a caregiver's lap and calmed and attached to the Masimo reference device. For the RR counters, 2 assessments were performed by the health workers and recorded, along with the corresponding Masimo reference measurements, and within 5 minutes of the health worker measurements, the ECs took 2 RR measurements using a stopwatch. For pulse oximeter devices, the health workers took 2 SpO_2 measurements, and the EC also took 2 SpO_2 measurements using the same pulse oximeter the health worker had used, along with simultaneous Masimo SpO_2 reference measurements. The health workers were asked to classify a child into fast or normal breathing using the WHO age-specific cut-offs for RR for RR devices or for severe or nonsevere pneumonia based on the SpO_2 reading being <90% for pulse oximeters.

In phase 2, to assess the usability and acceptability of the devices in routine practice by health workers and explore their acceptability to caregivers, field testing was conducted over 3 months. This was a mixed-methods study incorporating structured observations, video recordings of procedures, and qualitative exit interviews with health workers and caregivers. During the activity, 100 health workers were trained for 2 days to use an RR counter and a pulse oximeter as part of their routine iCCM or IMCI activity. Each health worker had to pass a competency-based assessment before participating in the data collection. The research team scheduled visits with each health worker 3 times (once a month) during the evaluation, each time gathering a minimum of 5 assessments of each CHW or FLHFW. The health workers took the medical history of children as per the iCCM or IMCI guidelines, and if cough and/or difficulty breathing were recorded, the health workers used the RR device to count the number of breaths in 1 minute; a procedure that was repeated twice, and the highest reading was used for classification. The observed RR was used by the health workers to decide whether or not to provide treatment for pneumonia using the national treatment guidelines. If fast breathing was detected, the health workers assessed for hypoxemia using the pulse oximeter by taking two SpO_2 readings and used the lowest reading for classification. All children with signs and symptoms of severe pneumonia and with SpO_2 <90% were referred.

Data Collection

Paper-based data collection tools were developed in local languages for both phases and collected data on screening, usability and performance, and adverse events. All data collection tools were developed in collaboration across the 4 research sites and were translated and pilot-tested in all locations before the start of the study. The tools for performance and usability included demographic information, child status, device measurement results, health worker classification of results, time taken, failures, and usability checklists. In addition, semistructured interview guides were developed for the exit interviews with caregivers and health workers (Multimedia Appendix 3). Video recordings and photographs of the health worker log books were captured as back-up to the paper forms submitted. All completed forms and log book photos were returned to the Malaria Consortium office for double data entry using EpiData version 3.1 (EpiData Association, Odense, Denmark) and filed. The qualitative data collection consisted of in-depth interviews with health workers at the end of data collection to capture their views on the usability and acceptability of the devices. Each data form had a unique identification code to link data from different forms in the database.

Data Analysis

The analysis of the primary outcome for phase 1, the agreement between each health worker measurement using the test device and that of the reference standards, was done following a per-protocol approach for each RR and SpO_2 measurement. Agreement was calculated as the proportion of observations that were within ±2 breaths or SpO_2% for each of the 9 devices, respectively, in the per-protocol population (only including children who had a cough and difficulty breathing and no danger signs). The secondary outcomes for the performance evaluation, the agreement in classification of the RR or SpO_2 obtained by health workers and the reference standards was measured using Cohen kappa statistic, positive percent agreement, and negative percent agreement of each device. For all of these secondary outcomes, the unit of analysis was the child rather than the device measurements. To illustrate the agreement between different devices, Bland-Altman plots [27] were produced to visualize the agreement in ratings of respiratory counts between reference standards and CHWs. The primary outcome for the usability and acceptability evaluation in phase 2 used qualitative analysis to establish the acceptability, based on users' perceptions of the different devices used. Secondary outcomes for the acceptability and usability evaluation included the proportion of users who accurately followed the correct procedures and the caregivers' perceptions of, interaction with, and reaction to the devices when used on children.

Results

This project was funded in 2014. Data collection started on February 4, 2015 and was completed on December 31, 2015. Data analysis is currently under way and the first results are expected to be submitted for publication in 2018.

Discussion

To reduce the number of child deaths from pneumonia in low-resource settings and to minimize unnecessary use of antibiotics, it is crucial to improve the diagnosis of pneumonia symptoms by frontline health workers [28]. This study aimed to meet this need by identifying possible improved pneumonia diagnostic devices and evaluated 9 of these in "real-life" health system contexts in 4 different countries in 2 continents. One of the key factors in designing a study like this is agreeing on the gold or reference standard to compare the devices to. The gold standard is the best single test (or a combination of tests) that is considered the current preferred method of diagnosing a particular disease [29]. Many possible gold standards have been suggested for RR timing devices in the literature, such as

simultaneous counting by a clinical expert [5], real-time electronic monitoring, or retrospective review of video recordings by a panel of experts [7,30]. However, all these methods have limitations such as the inaccuracy of human counters [30] and the inconsistency of counting between humans and electronic monitoring devices [30]. On review, and through discussions with experts from the WHO, UNICEF, and academia in the scientific advisory committee for the study, it was decided that no suitable gold standard exists in this setting; therefore, it was agreed to use 2 imperfect reference standards—the automated Masimo Root patient monitoring and connectivity platform with Radical-7 pulse oximeter and capnograph using Phasein ISA CO_2 module [26] and a simultaneous assessment by a clinical expert. Furthermore, it was hoped that using 2 different types of references, in the absence of a suitable gold standard, would best account for the limitations outlined above.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Complete scoring sheet for 188 possible pneumonia diagnostic aids, including respiratory rate timers, pulse oximeters and joint devices.

[XLS File (Microsoft Excel File), 264KB - resprot_v7i10e10191_app1.xls]

Multimedia Appendix 2

Summary of final devices tested in the field for performance, acceptability, and usability.

[PDF File (Adobe PDF File), 93KB - resprot_v7i10e10191_app2.pdf]

Multimedia Appendix 3

Discussion guide for caregiver interviews.

[PDF File (Adobe PDF File), 48KB - resprot_v7i10e10191_app3.pdf]

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Abbreviations

CHW: community health worker
EC: expert clinician
FLHFW: first-level health facility workers
iCCM: integrated community case management
IMCI: integrated management of childhood illness
RR: respiratory rate
UNICEF: United Nations Children's Fund

WHO: World Health Organization

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Original Paper

Co-Designing an eHealth Service for the Co-Care of Parkinson Disease: Explorative Study of Values and Challenges

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Abstract

Background: The need for services to support patient self-care and patient education has been emphasized for patients with chronic conditions. People with chronic conditions may spend many hours per year in health and social care services, but the majority of time is spent in self-care. This has implications in how health care is best organized. The term co-care specifically stresses the combination of health care professionals' and patients' resources, supported by appropriate (digital) tools for information exchange, to achieve the best possible health outcomes for patients. Developers of electronic health (eHealth) services need to consider both parties' specific needs for the service to be successful. Research on participants' experiences of participating in co-design sessions is scarce.

Objective: The aim of this study was to describe different stakeholders' (people with chronic conditions, health care professionals, and facilitators) overall experiences of participating in co-design workshops aimed at designing an eHealth service for co-care for Parkinson disease, with a particular focus on the perceptions of values and challenges of co-design as well as improvement suggestions.

Methods: We conducted 4 half-day co-design workshops with 7 people with Parkinson disease and 9 health care professionals. Data were collected during the workshop series using formative evaluations with participants and facilitators after each workshop, researchers' diary notes throughout the co-design process, and a Web-based questionnaire after the final workshop. Quantitative data from the questionnaire were analyzed using descriptive statistics. Qualitative data were triangulated and analyzed inductively using qualitative content analysis.

Results: Quantitative ratings showed that most participants had a positive general experience of the co-design workshops. Qualitative analysis resulted in 6 categories and 30 subcategories describing respondents' perceptions of the values and challenges of co-design and their improvement suggestions. The categories concerned (1) desire for more stakeholder variation; (2) imbalance in the collaboration between stakeholders; (3) time investment and commitment paradox; (4) desire for both flexibility and guidance; (5) relevant workshop content, but concerns about goal achievement; and (6) hopes and doubts about future care.

Conclusions: Based on the identified values and challenges, some paradoxical experiences were revealed, including (1) a desire to involve more stakeholders in co-design, while preferring to work in separate groups; (2) a desire for more preparation and discussions, while the required time investment was a concern; and (3) the experience that co-design is valuable for improving care, while there are doubts about the realization of co-care in practice. The value of co-design is not mainly about creating new services; it is about improving current practices to shape better care. The choice of methods needs to be adjusted to the stakeholder group and context, which will influence how they experience the process and outcomes of co-design.

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KEYWORDS

chronic conditions; co-design; eHealth; health care; mobile phone; Parkinson disease; qualitative research; questionnaire; self-care; user involvement

Introduction

The need for services to support patient self-care and patient education has been emphasized for patients with chronic conditions [1,2]. While people with chronic conditions may spend many hours in care, the majority of their time is spent in self-care. This calls for more patient-oriented and supported self-care services as well as a new type of collaborative partnership between patients and health care professionals [3,4]. The term co-care specifically stresses the need to combine health care professionals' and patients' resources for information exchange to achieve the best possible health outcomes for patients [5]. The use of electronic health (eHealth) tools—defined as the use of electronic means to deliver health-related information, resources, and services [6]—may be appropriate to support co-care. This paper describes the experiences of co-designing an eHealth service intended to support this type of partnership between people with chronic conditions, Parkinson disease in the specific context of this study, and health care professionals. A description of components of the intended eHealth service is beyond the scope of this paper.

Patient involvement in the improvement and development of health care services has been a key concept for many years. It has been suggested that health care services are necessarily coproduced by health care professionals and patients [4]. In parallel with coproduction, related terms, such as cocreation and co-design, have gained popularity in recent years [7]. Cocreation has been broadly defined as any act of collective creativity, while co-design signifies the span of a design process [7]. Co-design principles have been applied specifically in the development of eHealth services to support self-care in people with chronic conditions, such as in rheumatology [8], diabetes [9], oncology [10,11], and for family and carers of frail older adults [12].

Challenges and benefits of user involvement in the development of eHealth services have been described previously [13,14]. The evidence suggests a positive correlation between user involvement and system success [15]. However, research more often reports the results in terms of the service developed rather than how and to what extent the users were involved. The purpose, methods, and degree of user involvement may vary greatly between different projects. According to a structured review [16], user involvement in health care technology development is most common in the design phase of the system development lifecycle and the most common methods of user involvement include usability tests, interviews, and questionnaires, while other methods, such as design sessions or focus groups, are less common. We have identified 1 published paper that describes how experiences of co-design may differ based on team members' roles and backgrounds [17]. More research into this area, focusing on co-design experiences of various stakeholder groups—co-design participants as well as facilitators—may add further knowledge of methodological considerations that are needed to guide co-design projects.

The aim of this study was to describe different stakeholders' (people with chronic conditions, health care professionals, and facilitators) overall experiences of participating in co-design workshops aimed at designing an eHealth service for co-care for Parkinson disease, with a particular focus on the perceptions of values and challenges of co-design as well as improvement suggestions. The results of this study may support future research into the performance of co-design of eHealth services.

Methods

Study Design

We conducted 4 half-day co-design workshops in May and June 2016 to explore co-care needs among people with Parkinson disease (PwP) and health care professionals. The first 3 workshops aimed at capturing needs and generating ideas for the design of an eHealth service (see Multimedia Appendix 1). Between the 3rd and 4th workshops, a functional prototype was developed to visualize the ideas that had been discussed. In the 4th workshop, the prototype was demonstrated as a mobile app on a smartphone and tablet (for PwP), and as a Web application (for health care professionals). The demonstration was based on a fictive scenario that captured different functionalities in a patient-provider interaction. Acceptance and usability were discussed with workshop participants.

Mainly qualitative data, but also quantitative data, were collected during and after the workshops, reflecting participants' and facilitators' perceptions. This study is part of an action research project that involves multiple stakeholders (academia, health care organizations, and patient organizations) in designing, implementing, and developing models of co-care for people with chronic conditions. The regional ethical committee approved the study (2015/2216-31/5).

Participants

In this study, 7 PwP (Table 1) and 9 health care professionals (Table 2) specialized in neurology participated, together with 7 facilitators, were enrolled. All respondents reported using the Internet on a daily basis, and all but one of the PwP used a smartphone or a tablet in everyday life.

People with Parkinson Disease

The chairperson of the regional patient association for Parkinson disease sent an email to all registered members with a brief description of the research project. In total, 32 interested members contacted the researchers for further information. The ability to communicate in Swedish and availability for participation in all 4 workshops were the main criteria for inclusion. Variation in age, gender, and years since diagnosis were also considered. Eight PwP met the inclusion criteria and were recruited. Of these,1 dropped out prior to the first

workshop. The age of the 7 participating PwP ranged from 45 to 85 years (45, 56, 68, 73, 74, 74, and 85 years).

Health Care Professionals

A neurologist who is a member of the research group sent an email invitation to 19 experienced health care professionals. We anticipated the recruitment of different health care professionals who are involved in the care of Parkinson disease, targeting primarily neurologists, nurses, physiotherapists, and counselors. In total, 11 health care professionals expressed interest and availability to participate and were recruited. Of these, 2 dropped out prior to workshop initiation. The age of the 9 participating health care professionals ranged from 32 to 63 years (32, 40, 45, 46, 47, 55, 58, 61, and 63 years).

Briefly, 2 professional moderators and 5 researchers with previous experience of doing co-design work in health care planned and carried out the workshops. The researchers collected data during the workshops and assisted the moderators—3 postdoctoral researchers (2 with degrees in health informatics and 1 in physiotherapy), 1 doctoral student in health care management research, and 1 research assistant (a medical doctor with a degree in public health and health informatics). The workshop facilitators collaborated with a developer who was prepared to participate in the workshops if necessary. However, collaboration between the workshop sessions was considered sufficient.

Co-Design Workshops

Structure

All workshops were carried out in university facilities. Food and drinks were provided for free. The participants did not receive any other reimbursement for their participation. Each workshop was introduced by one of the researchers who informed participants about the aim and structure of the day and summarized previous achievements. The overall goals of the co-design workshops were presented as follows to the participants: (1) to identify co-care needs; (2) to agree on what an eHealth service for co-care should contain and how it should be used; and (3) to collaboratively generate ideas for an eHealth service.

The content of individual workshops was decided through an iterative process between, during, and after workshops. The facilitators used the breaks between workshop sessions to discuss progress and to decide on possible deviations from the planned schedule. At the end of each workshop, the facilitators met for a debriefing session. The researchers also sent emails to the participants to summarize achievements after each workshop. Multimedia Appendix 1 summarizes the specific aims and results of individual workshops.

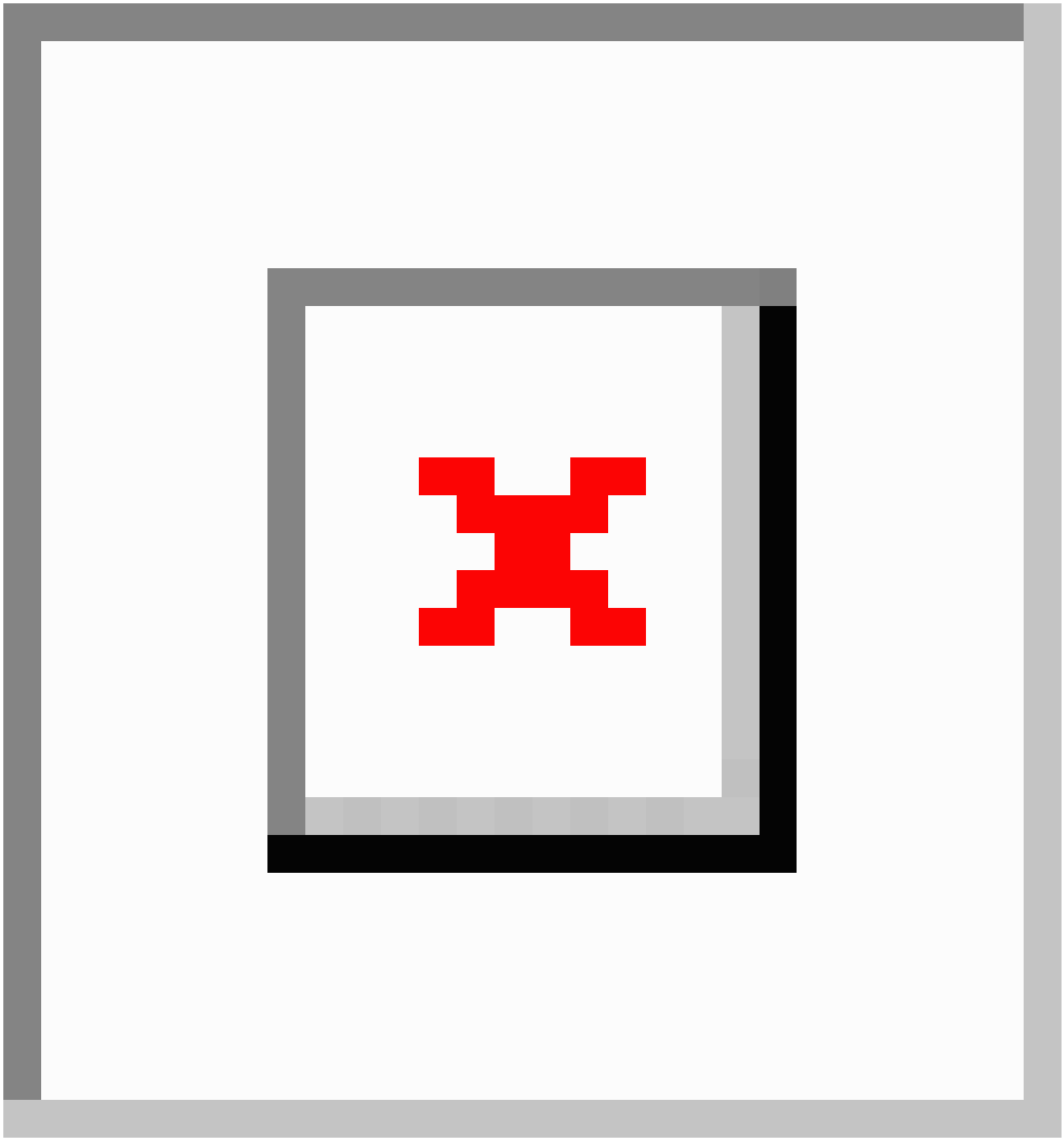
Table 1. Characteristics and workshop attendance of people with Parkinson disease.

Identifier	Gender	Occupation	Education level	Years since diagnosis	Participation			
					Workshop 1	Workshop 2	Workshop 3	Workshop 4
P1	Female	Pension	University	>10	Present	Present	Absent	Present
P2	Female	Pension	University	6-10	Present	Present	Present	Absent
P3	Female	Sick leave	University	>10	Present	Present	Present	Absent
P4	Female	Pension	University	>10	Present	Present	Absent	Present
P5	Male	Pension	PhD	6-10	Present	Present	Present	Present
P6	Male	Pension	PhD	1-5	Present	Present	Present	Present
P7	Male	Sick leave	High school	<1	Present	Present	Present	Present

Table 2. Characteristics and workshop attendance of health care professionals.

Identifier	Gender	Profession	Neurology experience (years)	Participation			
				Workshop 1	Workshop 2	Workshop 3	Workshop 4
H1	Female	Nurse	>10	Present	Present	Present	Present
H2	Female	Nurse	>10	Present	Present	Present	Absent
H3	Female	Nurse	>10	Present	Present	Present	Present
H4	Male	Physician	>10	Present	Present	Present	Absent
H5	Male	Physician	>10	Present	Absent	Absent	Absent
H6	Male	Physician	>10	Absent	Absent	Present	Present
H7	Female	Physician	>10	Absent	Absent	Present	Absent
H8	Female	Physiotherapist	>10	Present	Present	Present	Present
H9	Male	Physiotherapist	1-5	Present	Absent	Absent	Absent

Figure 1. Note cards reflecting participants' ideas in the co-design sessions.



Methods

The workshops contained co-design sessions and focus group discussions. The co-design sessions were used to generate, collect, and discuss ideas based on the nominal group technique [18]. First, participants were presented with a discussion question. Each participant got 3-5 note cards (depending on the question) on which they wrote down their individual reflections. The note cards were then collected and grouped according to similarities on a large canvas (Figure 1). Thereafter, a moderator led the discussion in which all individual cards were systematically discussed, rephrased, and regrouped. On 2 occasions (workshops 3 and 4), focus group discussions [19] were carried out in separate groups of PwP and health care professionals (see discussion guides in Multimedia Appendix 2).

Data Collection

We used 3 different instruments to collect data on participants' and facilitators' overall experiences, perceived values, and challenges of the co-design workshops and their improvement suggestions.

Formative Evaluations on Note Cards

Each individual workshop was formatively evaluated using 2 questions capturing perceived values, challenges, and improvement suggestions [20]: *What worked well?* and *What could be done differently?* The participants' feedback was collected anonymously on note cards. The facilitators provided

their feedback verbally in a debriefing session after each workshop while one of the researchers took notes.

Researchers' Diary

Throughout the co-design process, the researchers noted their reflections in a diary, in particular in connection with workshops and planning sessions. Unstructured diaries have been found to provide rich and in-depth data [21]. All researchers had access to the same electronic diary, and 3 of them wrote notes.

Summative Evaluation Using a Web-Based Questionnaire

After the final workshop, a Web-based questionnaire was distributed to all participants to collect data on their general experience of the workshops and their views on collaboration, participant contribution, and logistics. Questionnaires are a cost- and time-efficient data collection tool that offers anonymity [22]. The questionnaire in this study was designed as a structured interview guide with 7 open-ended questions, 2 ranking questions, and 2 yes or no questions (see Multimedia Appendix 3).

Data Analysis

Descriptive statistics were used to summarize participants' answers to 4 close-ended questions in the Web-based questionnaire, reporting percentages for the yes or no questions and the mean and range for ranking questions. Qualitative data were compiled into text documents and analyzed inductively according to principles of qualitative content analysis described elsewhere [23]. All authors read through the text. Then, 2 authors per data source coded the text separately and met to discuss and consolidate their codes. The codes (n=408) were printed out on paper slips and categorized manually. When an agreement had been reached by discussion between the researchers, the categories were transferred into mind-mapping software (FreeMind version 1.0.1) together with their constituent codes. The categorization was refined in several iterations until satisfaction was reached. Categories and subcategories were labeled to reflect the content of their constituent codes. Finally, the underlying meanings of categories were discussed, and themes were formulated. Illustrative quotes were selected to present in the results. An example of the data abstraction is presented in Multimedia Appendix 4.

Results

Participants' Overall Experiences of the Co-Design Workshops

The results of quantitative analysis show that 75% (12/16) of the participants completed the questionnaire (6 of them after a reminder). All participant roles were represented—5 PwP, 3 nurses, 2 physiotherapists, and 2 physicians. The results indicated that the participants who completed the questionnaire had a positive experience regarding the co-design workshops (Table 3).

Perceived Values, Challenges, and Suggestions for Improvements

Dataset for qualitative content analysis comprised 3 data sources as follows: (1) approximately 3000 words of diary notes from 3 researchers; (2) 165 formative workshop evaluation comments—75 of them from facilitators (based on workshops 1-4) and 92 from participants (based on workshops 1-3); and (3) 111 open-ended questionnaire responses from participants. Briefly, 6 categories and 30 subcategories that capture perceived values, challenges, and improvement suggestions were identified (Textbox 1). The 6 categories are described below, supported by illustrative quotes (translated from Swedish to English). Each quote is referenced with a unique identifier, composed of its source (wwdd: worked well; do differently feedback; d: diary; q: Web-based questionnaire) and a sequential number. In the text that follows, the descriptor *participants* refers to PwP and health care professionals; *facilitators* refers to the researchers and moderators; and *respondents* is used as an umbrella term for participants and facilitators. Individual roles, such as PwP and health care professionals, are distinguished where possible, although not for quotes from the formative feedback that was collected anonymously.

Desire for More Stakeholder Variation

The participants were positive about the constellation of workshop participants, representing individuals with different backgrounds and competences. They particularly valued listening to other individuals' perspectives and opinions about care and expressed that more diversity of experiences and expertise would have been beneficial. In particular, they desired the involvement of informal caregivers and representatives from additional care professions as well as a larger PwP group with more variation in the disease status. This is reflected in the following participant quotes:

> *A pity there wasn't more disease variation in the participants with Parkinson disease.* [wwdd.188]
>
> *Miss representatives from all care professions.* [wwdd.187]

Table 3. Results of 4 close-ended questions in the Web-based questionnaire.

Question	All participants (n=12)	PwP[a] (n=5)	Health care professional (n=7)
"What was your overall experience of participating in the workshop series?"[b], mean (range)	7.9 (7-9)	7.8 (7-8)	7.4 (6-9)
"In your opinion, was the workshop content in line with the aim; to develop a co-care service?"[c] (yes), n (%)	12 (100)	5 (100)	7 (100)
"To what extent did you perceive that your voice was heard?"[d], mean (range)	4.3 (2-5)	4 (3-5)	4.4 (2-5)
"In your opinion, was there was a balance between how much the participants with Parkinson disease and healthcare professionals voiced their thoughts?"[c] (yes), n (%)	9 (75)	5 (100)	4 (57)

[a]PwP: people with Parkinson disease.

[b]Response scale: 1-10 (1=worst possible experience, 10=best possible experience).

[c]Response scale: yes or no.

[b]Response scale: 1-5 (1=Not at all, 5=Always).

Textbox 1. Categories and subcategories describing participants' perceived values and challenges of co-design and improvement suggestions.

Desire for more stakeholder variation (represented by participants only, P)

- Good participant constellation (P)
- Need for more diversity in expertise and experiences (P)
- Need for several representatives of individual stakeholder groups (P)

Imbalance in the collaboration among multiple stakeholders with diverse backgrounds and expectations

- Dynamic and pleasant discussion climate
- Engaged and active participants
- Differences in how much participants express their opinions
- Stakeholders managed to make their voices heard
- Communication difficulties due to differences in knowledge, roles, and expectations
- Need to balance participant activity

Time investment and commitment paradox

- Need for additional and longer workshops and more time for preparation
- Time-consuming process (P)
- Need to address patients' health-related challenges
- Challenging to achieve long-term commitment among participants and researchers
- Need to communicate with participants before and between workshops (represented by facilitators only, F)

Desire for both flexibility and guidance from facilitators

- Need for dynamic and flexible facilitation
- Need for clearer roles and responsibilities among facilitators (F)
- Need for adequate methods for data collection during the workshops (F)
- Important to focus discussions using guidance
- Important to have good time management
- Provide clarity with appropriate tools and content
- Important to prepare the workshop setting

Relevant workshop content, but concerns about goal achievement

- General positive experiences
- Interesting and educational (P)
- Good to discuss reality and vision of care (P)
- Fun and important to co-create (P)
- Concern about workshop alignment (F)
- Inconsistent goal achievement

Hopes and doubts about future care

- Co-design creates hope for the future
- Long way to usability (P)
- Concern about health care's readiness for co-care services

Imbalance in the Collaboration Among Stakeholders With Diverse Backgrounds and Expectations

On the one hand, respondents perceived that the discussion climate was dynamic and pleasant and that the participants were engaged and had a high energy level. On the other hand, they perceived that there was an imbalance in participants' influence. Care professionals were more active in expressing their opinions, sometimes on behalf of PwP. The respondents expressed communication difficulties related to differences in knowledge

and expectations about care and the health care professionals' use of specific language that was sometimes difficult to understand for PwP. Care professionals felt that they got too much attention, but as one of them commented, "Despite imbalance, the patient group was strong and dared to contribute" (q.82). The facilitators pointed out the importance of being aware of power relationships, managing participants who dominate, and enabling silent participants (mainly PwP representatives) to speak up. One of the facilitators commented that "it felt like more participants got the chance to speak during the focus groups, which resulted in a more nuanced understanding" (d.92). This was confirmed by the participants, who favored the focus group discussions, as illustrated in the following quote by a PwP: "Maybe better with more discussions in separate groups" (q.70).

Time Investment and Commitment Paradox

The participants expressed a need for more time for the co-design process. They commented that more and, perhaps, longer workshops may have been beneficial. At the same time, the facilitators reflected that some of the sessions lasted too long for the participants to keep their concentration. Apart from sufficient time to collaborate in workshops, both participants and facilitators emphasized time for preparation. As a participant stated, "More time for preparation before the workshops enables us to contribute more" (wwdd.182). Meanwhile, the participants also expressed that the considerable investment of time that was required to engage in co-design was a major concern. Moreover, a care professional pointed out the need to consider health-related issues of PwP: "it would maybe have been better for patients to attend the workshops later during the day" (q.61). Facilitators noted that attendance was inconsistent for participants and for nonparticipant observers (ie, the researchers), and they reflected on how they could enhance the chances of keeping participants engaged, such as by socializing with them during breaks and maintaining contact between the workshops. Communication between workshops was appreciated by participants, as illustrated in the following quotes from health care professionals: "Useful informative mails" (q.96) and "Good to receive summaries between the workshops" (q.97).

Desire for Both Flexibility and Guidance From Facilitators

The respondents appreciated that the moderator was dynamic and flexible and adjusted the workshop content and structure to meet participants' needs. As one of the health care professionals commented, "We created a structure together" (q.15). While flexibility was necessary, the facilitators recognized the need for clear roles and responsibilities and well-functioning communication channels in the team, which would also facilitate data collection for the observers. The participants appreciated when discussions were guided by concrete questions, and they emphasized the need to allow sufficient time for discussions. As one of them suggested, "Limit the scope of the tasks more in the workshops" (wwdd.179). The facilitators' reflections indicate that they sometimes struggled with the selection of appropriate co-design methods that would support the design of an eHealth service. The participants appreciated working with note cards as they perceived that these provided a good overview of what was discussed. Furthermore, one of the facilitators reflected that "the prototype was probably key in clarifying the co-care concept" (d.103). The choice of workshop setting, characterized by sufficient space, ventilated rooms, and well-functioning technical equipment, was considered important to provide good conditions for the co-design process.

Relevant Workshop Content, but Concerns About Goal Achievement

The respondents shared positive experiences about the overall workshop performance, preparations, flow, logistics, structure, and teamwork. The participants perceived that the workshop content was interesting and educational, particularly when discussing the reality, expectations, and vision of care. As a participant commented, "I have a better understanding now. The workshops have helped me to reflect on the health care system in a new way" (wwdd.138). Co-design was perceived as fun and important, and one of the health care professionals noted that "It is important to develop the co-care service together to increase the chance of future use" (q.31). On the other hand, the respondents expressed concern about goal achievement, and the facilitators were concerned about succeeding in workshop alignment and ensuring progression. One of the facilitators reflected after the second workshop, "There is some concern among both the project team and participants about where we are headed" (d.42).

Hopes and Doubts About Future Co-Care

The respondents perceived that co-design creates hope for future care. For example, one of the participants commented on the result of the co-design workshops (ie, the eHealth prototype): "the content is promising and has potential to improve follow-up [as in continuity] of care" (wwdd.79). Nevertheless, they also realized that there is a long way to go before actual use. As one of the PwP expressed, "We took the first steps, but we have a long way to go" (q.67). The participants voiced concerns about health care's readiness for co-care services, and one of the PwP highlighted that it is "important to engage health care" (q.106). Their concerns were that administration of a new eHealth service would take too much time and cause stress for personnel or reduce the time available for patient encounters.

Discussion

Principal Findings

This study explored different stakeholders' (PwP, health care professionals, and facilitators) overall experiences of participating in co-design workshops aimed at designing an eHealth service for co-care of Parkinson disease, with a particular focus on their perceptions of the values and challenges of co-design as well as improvement suggestions. The participants had an overall positive experience of the co-design workshops. The values and challenges were identified across 6 different domains, covering, multistakeholder involvement and collaboration, time investment and commitment, flexibility and guidance from facilitators, goal achievement, and reflections on future care. A deeper analysis of the results revealed paradoxical patterns in some of the experiences, namely the

following: (1) a desire to involve more stakeholders in co-design, while preferring to work in separate groups; (2) a desire for more preparation and discussions, while the required time investment was a concern; and (3) the experience that co-design is valuable for improving care, while there are doubts about the realization of co-care in practice. These paradoxes are further discussed below.

Desire to Involve More Stakeholders While Preferring to Work in Separate Groups

The selection and recruitment of participants for the co-design workshops was a challenge because we aimed to involve diverse stakeholders, while maintaining a sensibly sized co-design group for optimal collaboration. Pearce et al describe 4 phases of user involvement: *identification*, *engagement*, *recruitment*, and *retention* [24]. We had a PwP representative and a neurologist in the project group to help us with the identification and recruitment of participants who represented central stakeholders. Informal caregivers were identified as an important stakeholder group, which was also emphasized by the participants' feedback. The need for better support for informal caregivers has also been recognized in previous research, as they have an important role in the care of PwP [25]. However, the involvement of informal caregivers with no personal relationships with participating PwP was challenging in this study, mainly due to the timing of the workshops, which was during working hours. Furthermore, the involvement of additional stakeholders may have made it more challenging to collaborate.

While the participants' questionnaire ratings in this study indicate that they experienced their voices being heard to a high extent and that participants' activities were balanced, the qualitative analysis, nevertheless, indicates that health care professionals experienced that they talked too much and even spoke on behalf of PwP. This may be explained by inherent asymmetric power relationships between patients and health care professionals. The power of health care professionals has been suggested to be activated in the interaction with patients [26]. However, based on previous experiences of co-design projects with multiple stakeholders [8], the involvement of both health care professionals and patients does not necessarily inhibit patients from speaking up. During the workshop process, we became aware that there was not just a theoretical power asymmetry in the co-design group, but that there were actual patient-professional relationships among the participants. This may have hindered PwP in voicing their opinions due to the fear of possible negative consequences to their care. A good personal relationship between patients and physicians is important and has an impact on both diagnosis and treatment [27,28]. In addition, it became clear from the participants' feedback that they appreciated and likely preferred discussions in separate groups, which may also be related to the relationship issues and power asymmetry. However, some valuable information and design ideas may only result from the interaction between the PwP and health care professionals. Thus, facilitators need to find measures to actively handle power asymmetries, similar to what has been suggested for physicians in encounters with their patients [26]. More research may be needed to expand the knowledge of potential benefits and challenges of multistakeholder collaboration in different phases of co-design. This may also require an in-depth discussion of the different stakeholder roles in co-design, including the facilitators' roles, power relationships, and implications of partnership in co-design and co-care.

Desire for More Preparation and Discussions While the Required Time Investment Was a Concern

A challenge experienced by the facilitators concerned the planning of co-design workshops to enable participants to engage in and commit to the entire co-design process, addressing the engagement and retaining phases of participant involvement [24]. The participants expressed concern about the co-design process being time-consuming, which is a well-known challenge of co-design [13,17,29]. During recruitment, it was particularly difficult to find health care professionals who could attend all 4 workshops, which is consistent with findings of previous research [30]. In this study, 2 of the participating health care professionals missed the first 2 workshops, which may have caused disruptions to the co-design process as they did not have the same level of understanding of the subject matter as did the other participants. However, we did not take note of such challenges. Some of the health care professionals pointed out that it was difficult for them to take time from their regular working hours. Various ways to engage participants must, therefore, be considered. In this study, we primarily used email to communicate with the participants between meetings to provide summaries from previous workshops and a plan for the next one. This was highly appreciated by the participants and enabled them to stay informed even though some of them could not attend all the workshops. Organization of additional face-to-face meetings [17] or the use of electronic means [31] has been previously discussed as a means to improve participants' engagement. A Web-based discussion forum would enable participants to contribute their ideas or reflections throughout the co-design process. Web broadcasting in combination with a discussion forum would also enable participation from abroad. Furthermore, more silent participants could get an option to contribute their ideas electronically.

Experience That Co-Design Is Valuable for Improving Care While Doubts About the Realization of Co-Care in Practice Are Maintained

The participants in our project raised concerns about the long way yet to go before a usable product is ready and doubts about health cares' readiness for co-care. Previous research reports the positive impact of user involvement on system success [15,29,32-34], which may be the main driver for contributing to co-design. However, the co-design process in our project was too short for the participants to get a return on their investment of time and effort. We experienced that the main value for participants was having the opportunity to share knowledge and experiences with others and being able to contribute to the improvement of health care. Previous research has discussed that the coproduction of public services may be experienced as both empowering and exploiting by participants [35]. How to reward participant contributions and deal with intellectual property in co-design projects is not straightforward, especially if for-profit organizations are involved in the operationalization of design ideas into products and services. It is important to

clarify from the beginning what results participants can expect [24] to mitigate the risk of disappointment or worse, a feeling of being exploited.

Strengths and Limitations

The main strength of this study was the triangulation of multiple data sources collected at different timepoints to capture participants' and facilitators' experiences and perceptions during the co-design process. However, the data collection instruments were limited in their ability to collect in-depth data. Maybe some of the identified values and challenges were induced by the questionnaire and would not have been equally prominent if we had given the participants the opportunity to reflect more openly, such as in an interview or focus group discussion. In contrast, the diary notes from the researchers contained more in-depth reflections. Quantitative results from the questionnaire need to be interpreted with caution as the number of participants was limited and as the questionnaire was not based on previously validated items. Furthermore, variation in the degree of workshop attendance among participants may have influenced their responses.

The participation of 4 nonparticipant observers in each workshop, 1 in each corner of the room, allowed the researchers to observe group dynamics, which was important in the analysis process, even though observation notes were not included in the unit of analysis. The number of observers needs to be balanced with the risk that observation may influence participants, such as by leading them toward introspection or even questioning their own behavior [36].

Transferability

The transferability of our findings is largely dependent on the context and how co-design is applied in the service development. There is no one-size-fits-all model [37]. The use of different approaches in different contexts naturally limits transferability. Nevertheless, we believe that our findings capture the general experiences of co-design (ie, the values and challenges that participants and researchers may experience) largely independent of the co-design aim and methods used. We have provided a rich description of our co-design process and participant characteristics to make it easier for readers to determine which of our findings may be applicable to their context. PwP in this study were on average very well educated, which may reveal an unintended selection bias. Possibly, mainly well-educated individuals felt confident to be able to participate in the project, which may also have been influenced by the location of the workshops in university facilities. We conclude that in the next phases of the project, the research team should identify other channels of participant recruitment that may lead to increased variation in participants with regard to sociodemographic factors, in general, as well as severity of disease.

Conclusions

Our findings concerning participants' and facilitators' experiences of co-design are paradoxical in many ways. To generate value from co-design, the choice of methods needs to be well adjusted to the stakeholder group and to the context, which will influence how participants experience the process and outcome. Importantly, co-design is only a phase in the cocreation and coproduction of better health care, and its potential can only be realized if the generated ideas are implemented in practice. Hence, the co-design process should involve a plan for the continued engagement of stakeholders throughout the implementation process. The findings from our co-design workshops support a general need for co-care services. However, we conclude that co-design is not mainly about creating new services, but it is about improving current practices to shape better care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Aims and main results of each of the 4 workshops performed during the co-design process.

[PDF File (Adobe PDF File), 94KB - resprot_v7i10e11278_app1.pdf]

Multimedia Appendix 2

Focus group discussion guides used in workshops 3 and 4.

[PDF File (Adobe PDF File), 46KB - resprot_v7i10e11278_app2.pdf]

Multimedia Appendix 3

The Web-based questionnaire sent out to participants after the final co-design workshop.

[PDF File (Adobe PDF File), 25KB - resprot_v7i10e11278_app3.pdf]

Multimedia Appendix 4

Data abstraction examples.

[PDF File (Adobe PDF File), 42KB - resprot_v7i10e11278_app4.pdf]

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Abbreviations

eHealth: electronic health
PwP: people with Parkinson disease

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Protocol

Innovative Approach for Enhancing Testing of HIV, Hepatitis B, and Hepatitis C in the General Population: Protocol for an Acceptability and Feasibility Study (BaroTest 2016)

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Abstract

Background: Despite substantial screening for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) infections in France, a great number of infected persons remain undiagnosed. In this context, Santé publique France experimented with a new screening approach for HBV, HCV, and HIV infection, based on home self-sampling using dried blood spot (DBS) for blood collection.

Objective: The objectives of the BaroTest study were to assess the acceptability and feasibility of this approach and to update the prevalence estimates of HBV, HCV, and HIV infections in the general population.

Methods: Participants were enrolled using the 2016 Health Barometer, a national cross-sectional telephone survey based on a large representative sample of the general population aged 15 to 75 years (N=15,000). Upon completion of the questionnaire, any participant in the Health Barometer aged 18 to 75 years, having medical health insurance, and not under guardianship was invited to receive a self-sampling kit delivered by standard postal mail and to return the DBS card to the laboratory. The laboratory was then responsible for reporting the results to the participants. Acceptability of the protocol was based on the percentage of eligible individuals agreeing to receive the self-sampling kit, on the proportion of people returning the DBS card, and on the proportion of participants out of the total eligible population. The feasibility of the approach was based on the number of participants with adequately filled blood spots and the number of participants with blood spots for which at least one virological analysis could be performed. A complex system of reminders was implemented to increase the participation rate. Accordingly, we assumed that 35.00% (4900/14,000) of eligible persons would accept and return their DBS card. As the highest expected prevalence was for HBV infection, estimated at 0.65% in 2004, 5000 persons would make it possible to estimate this prevalence with an accuracy of approximately 0.22%. All indicators can be analyzed according to the characteristics of the participants collected in the Health Barometer questionnaire. BaroTest was approved by the French Ethics Committee (November 11, 2015) and the Commission on Information Technology and Liberties (December 24, 2015). The study has been registered by the French medical authority under number 2015-A01252-47 on November 10, 2015.

Results: The results on acceptability and feasibility are expected in the last quarter of 2018 and those on the prevalence estimates in the first semester of 2019.

Conclusions: The BaroTest results will help to inform new strategies for HIV, HBV, and HCV screening, and the Health Barometer provides a reliable updated assessment of the burden of HBV, HCV, and HIV infections in the general population in France while reducing the costs typically associated with this type of research.

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KEYWORDS

home self-sampling; dried blood spot testing; feasibility studies; HIV infections; hepatitis B; hepatitis C; cross-sectional studies

Introduction

France is a low-endemic country for HIV infection, chronic hepatitis B virus (HBV), and chronic hepatitis C virus (HCV) infections, with prevalence in the general population estimated at 0.29% (in 2013), 0.65% (in 2004), and 0.42% (in 2011), respectively [1-3]. Prevalence of these infections is greater in subgroups at risk. For example, HIV prevalence was 17% in a community sample of men who have sex with men (MSM) in Paris [4], 13% among intravenous drug users [5], and 1.6% among Afro-Caribbeans living in the greater Paris area [6]. Anti-hepatitis B core antibody prevalence increased with the hepatitis B virus surface antigen (HBsAg) endemic level of the country of birth and was higher in the individuals with a history of intravenous drug use (50.1%) and among MSM (29.4%) [2]. The anti-HCV prevalence varied from 63.8% among people who reported ever injecting a drug and 1.8% among immigrants [3].

Screening activity is substantial; the annual rate of tests performed in public and private medical laboratories being 58 per 1000 inhabitants for HBV, 55 per 1000 inhabitants for HCV, and 80 per 1000 inhabitants for HIV [7,8]. Screening has expanded in recent years, with the introduction of rapid diagnostic tests performed by nonmedical staff (since 2012 for HIV, since 2016 for HCV, and in 2018 for HBV). However, a great number of infected persons remain undiagnosed, estimated at 155,000 people in 2004 for HBV, 74,000 in 2014 for HCV, and 24,800 in 2013 for HIV [9-11]. Accordingly, they do not benefit from the currently available effective antiviral treatments. Indeed, since 2014, direct-acting antivirals (DAAs) represent a major turning point in the treatment of hepatitis C, with more than 90% of treated patients being cured [12]. Access to DAAs is now free for all HCV-infected patients in France, irrespective of liver fibrosis stage, and this raises the hope that the epidemic will be controlled in the medium term in the country. Antiviral treatments for HIV and HBV keep viral replication under control in the majority of infected patients. Achieving sustained virological response with DAAs for hepatitis C and maintaining an undetectable viral load with HBV or HIV treatment are essential steps to reducing the risk of morbidity and mortality and to preventing the risk of transmission [13-15].

French screening strategies have been modified in recent years to foster earlier screening for HIV, HBV, and HCV infections and reach populations unaware of their infection. Recommendations strengthened the frequency of HIV screening in the key populations (eg, HIV testing every 3 months for MSM, once a year for drug users and migrants from sub-Saharan Africa). In addition, a complementary approach to screening in key populations was implemented to enable people who are unaware of their infection to be diagnosed and to reduce the hidden epidemic. The HIV, HBV, and HCV testing *at least once in the lifetime* is now proposed to individuals aged 15 years irrespective of their exposure risk (universal screening) [16]. Since 2014, combined screening for HIV, HBV, and HCV infections has also been recommended [17]. In this context, Santé publique France, the national public health agency, experimented with a new combined screening approach for HBV, HCV, and HIV infections, based on home self-sampling using the dried blood spot (DBS) for blood collection with the *BaroTest* study.

Methods

Objective

The primary objective of the *BaroTest* study was to assess the acceptability and feasibility of screening for HBV, HCV, and HIV infections using home-based self-collected blood samples on filter paper.

The secondary objective was to update the prevalence estimates of HBV, HCV, and HIV infections as well as undiagnosed infections in the general population.

Sampling and Study Enrollment

Participants were enrolled using the 2016 Health Barometer, a national cross-sectional telephone survey based on a representative random sample of the general population (15,000 individuals) aged 15 to 75 years living in mainland France (Figures 1 and 2).

The sampling method for the 2016 edition was identical to that developed for the 2014 Health Barometer [18]. Fixed-line and mobile phone numbers were randomly generated, with 1 individual being randomly selected from eligible members of the household. If the selected person agreed to answer the questionnaire, a unique 9-digit Health Barometer identifier was attributed to them. In case of refusal, the selected individuals and their household were not replaced.

The 40-minute-long phone survey questionnaire was administered by a trained investigator. It included questions evaluating general health, hygiene and protective habits, sexual and preventive behaviors, contraception, knowledge of vector-borne diseases and their prevention, opinions and attitudes toward vaccination, and attitudes toward HBV, HCV, and HIV screening.

Figure 1. Operational flowchart, BaroTest Study, 2016. EIA: enzyme immunoassay; GP: general practitioner; HCV: hepatitis C virus.

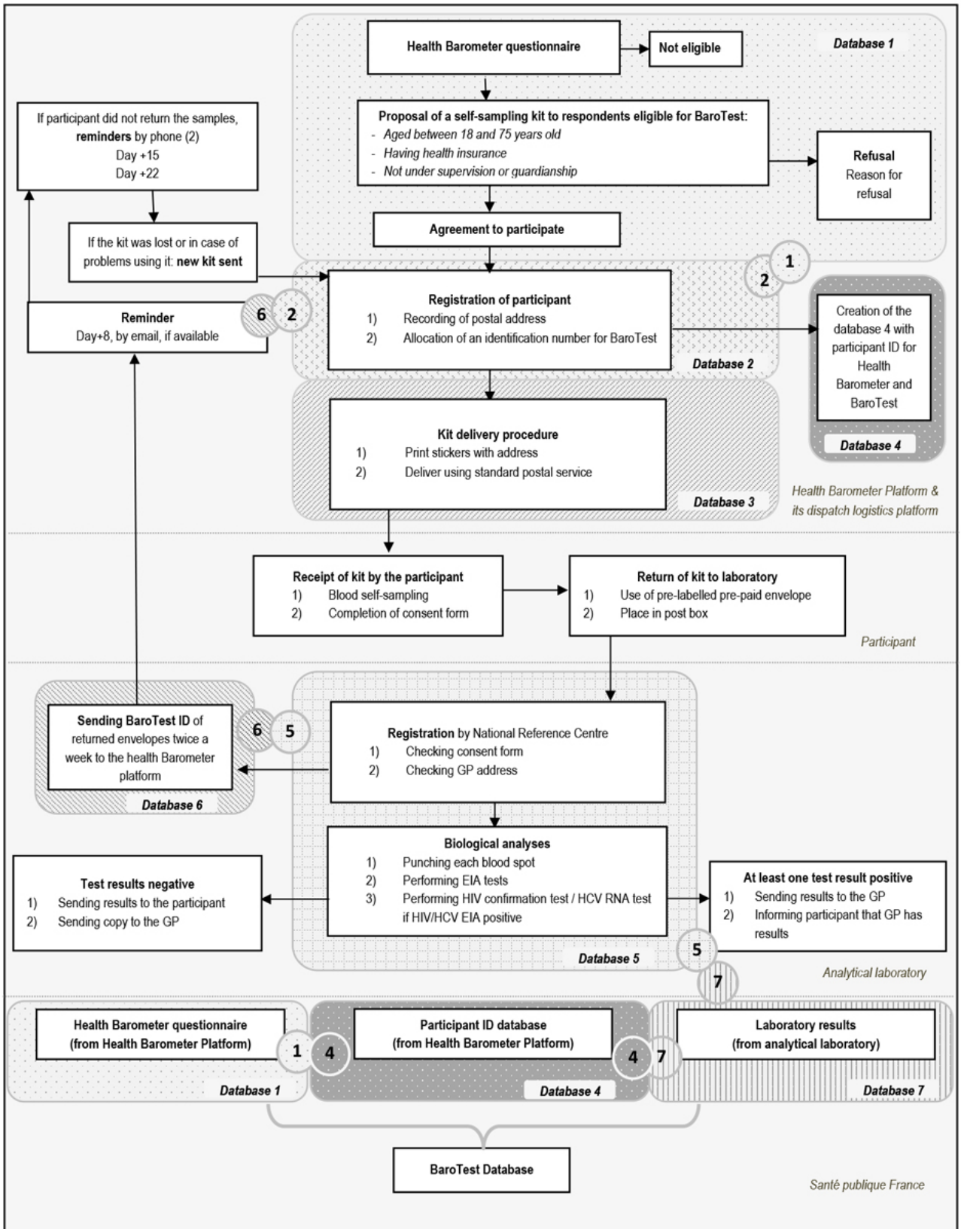
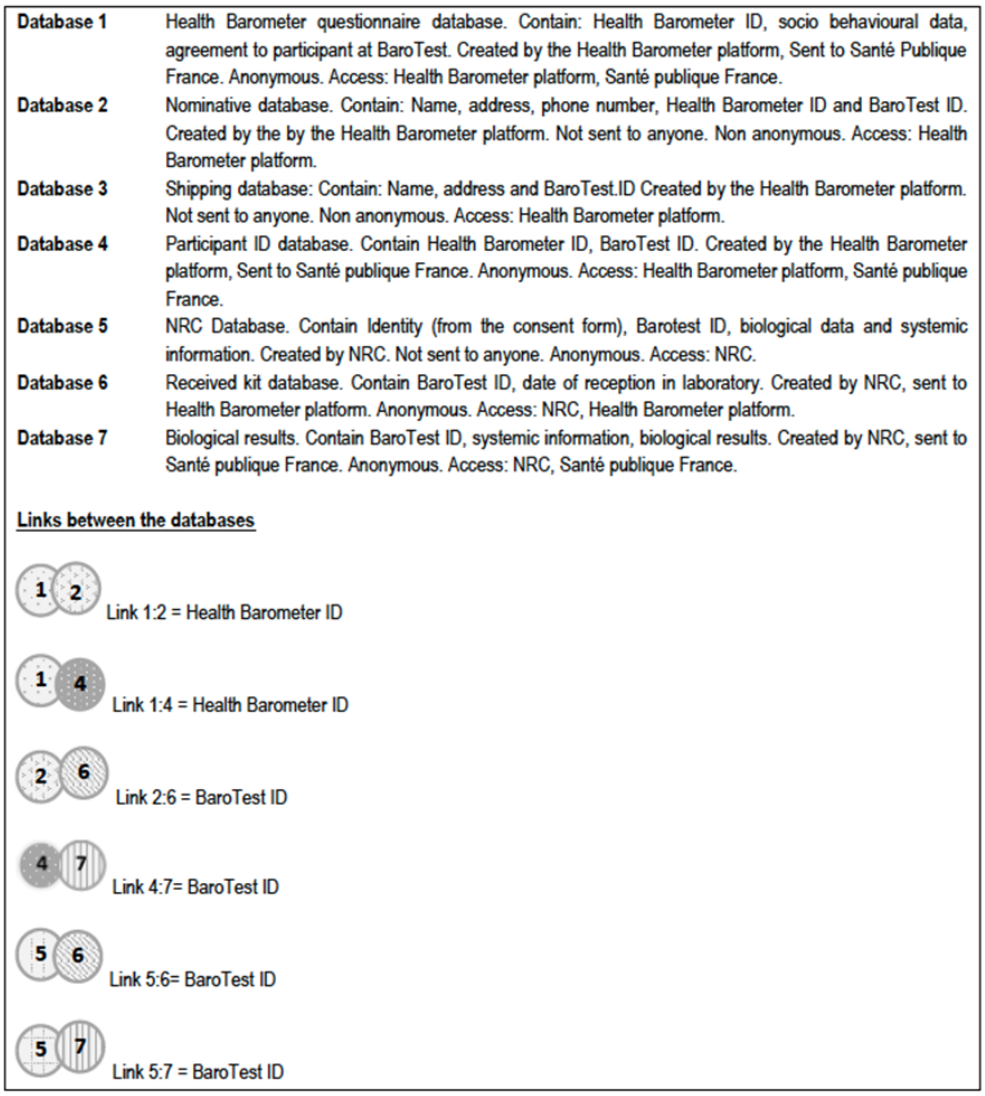


Figure 2. Legend for flowchart in Figure 1.



Study Population

Any participant in the 2016 Health Barometer aged 18 to 75 years, having medical health insurance, and not under guardianship was eligible for the BaroTest study.

Study Design

Upon completion of the Barometer phone–based questionnaire, all those eligible for BaroTest were invited to receive a self-sampling kit for HBV, HCV, and HIV testing delivered by standard postal mail.

The collective and individual benefits of screening, as well as the overall objectives of the survey were explained. When a participant declined this invitation, the reason was recorded. If accepted, the investigator:

- registered the first name and surname of the participant, along with the address to which the self-sampling kit would be sent;
- informed the participant that personal information would be recorded separately from information collected during the phone questionnaire and would only be retained for the period covering the delivery of the self-sampling kit, home self-sampling, and the return of the sample to the laboratory for testing;
- invited the participant to provide an email address and a telephone number so that a reminder could be sent in case the laboratory did not receive the dried blood sample card within 15 days of the dispatch date of the kit; and
- provided the participant with a telephone number and an email to be used to contact the investigator, in case of nonreceipt of the kit, difficulties with its use, or for any other issues concerning the study.

Textbox 1. Components of the kit.

- An information letter outlining the objectives and details on voluntary participation in the BaroTest. This letter also listed the telephone numbers of various helplines (AIDS Info Service and Hepatitis Info Service) for any questions related to HIV or AIDS, hepatitis B virus (HBV), and hepatitis C virus (HCV)
- A 2-page consent form to be signed and completed with the participant's name, date of birth, postal address to receive the results of the tests, and the contact details of a general practitioner (GP) of his or her choice to whom the results would also be sent
- The self-sampling kit, with detailed instructions for blood-sample collection; 2 single-use safety lancets; a prenumbered filter paper card (Whatman 903 FTA cards) with 5 preprinted circles zones, named spots (diameter: 6 mm); a disinfection cotton pad; and a small adhesive sensitive skin bandage
- A sealable plastic bag to protect the dried blood spot (DBS) including a desiccant packet to remove any moisture from the DBS card
- A bubble pouch for the 2 lancets to be returned with the DBS to ensure elimination of clinical infectious waste
- A prestamped and preprinted rip-resistant envelope addressed to the National Reference Centre (NRC), the laboratory in charge of HIV, HCV, and HBV analyses

The BaroTest participant was randomly assigned a prenumbered self-sampling kit, thereby defining his or her identifier number in the study (BaroTest ID). The kit was sent inside a resealable cardboard box in a large and plain envelope within 3 days of the completion of the Barometer questionnaire (Textbox 1).

After receiving the kit, the participant performed a capillary whole-blood sampling procedure by drawing blood from the fingertip with the lancet and depositing 1 large drop of free-flowing blood onto each of the 5 preprinted circles on the card, named *spots*. A spot is the area within the 6-mm diameter circle that is supposed to be filled with blood.

Once the self-sampling was performed and the blood sample card dried at room temperature (at least 3 hours), the participant inserted the DBS card into the sealable plastic bag with the desiccant packet, put the closed plastic bag into the resealable cardboard box along with the completed signed informed consent form and the bubble pouch with the 2 lancets, put the cardboard box in the return rip-resistant envelope, and sent it by mail to the National Reference Centre (NRC). Packaging and shipping followed international shipping guidelines and regulations for the Transport of Infectious Substances (WHO/HSE/GCR/2012.12).

The phone numbers of the HIV or AIDS and viral hepatitis national hotlines were mentioned in the consent form of the participants. These hotlines are open every day throughout the year. The staff was trained to address any sexual health question, including the topic of violence. The respondents were trained before the survey to answer any basic questions regarding the study. In addition, a study-specific email address was opened to the participants during the study to contact the study coordinator for any difficult question and to manage any adverse event that was transmitted via the hotlines.

Reception and Analyses of the Dried Blood Spot

Upon receipt of the envelope at the NRC, the following data were recorded in the NRC database: the BaroTest ID, the date of receipt, the name and address of the participant, the name and address of the general practitioner (GP), the status of the consent form (enclosed or not, signed or not, completed or not), and status of the DBS card (enclosed or not filled or unfilled). The DBS cards were assessed by a trained laboratory technician for both validity and amount of blood. The number of spots categorized as *empty*, *correctly filled*, or *incorrectly filled* was recorded in the NRC database.

Hepatitis B and C serological tests were based on the detection of the HBsAg and total anti-HCV antibodies, respectively. For this purpose, a single spot was eluted in 1 mL phosphate buffered saline with gentle agitation for 1 hour at 4°C and then centrifuged at 36,220 *g* for 1 min before use.

Qualitative HBsAg detection was performed by means of an automated enzyme immunoassay (EIA; VIDAS HBsAg Ultra, BioMerieux, France).

Detection of total anti-HCV was conducted by means of a third-generation EIA (aHCV Vitros ECi, Ortho-Clinical Diagnostics, Raritan, New Jersey, USA). If anti-HCV was positive, HCV RNA was detected with the Abbott RealTime HCV assay (Abbott Molecular, Des Plaines, Illinois), a real-time polymerase chain reaction–based method. Briefly, a second 6-mm spot was eluted into 1.5 mL Lysis buffer from Abbott at 56°C with gentle agitation for 30 min and then centrifuged at 36,220 g for 1 min before use.

For HIV analyses, a punch, 6 mm in diameter, from the DBS was placed in 150 µL of 0.01 M sodium phosphate buffer containing 10% bovine serum albumin and 0.05% Tween 20 (PBS-BSA-TW) and then incubated overnight at 4°C. The BioRad fourth-generation enzyme-linked immunosorbent assay (ELISA; Genscreen Ultra HIV Ag-Ab combo assay) was used to detect both anti-HIV and p24 antigen. The eluted samples were directly transferred to ELISA microplates (75 µL per well). Subsequent steps were performed according to the manufacturer's recommendations.

If the HIV test proved positive, a confirmatory test (Western Blot, HIV Blot 2.2, or MP Diagnostics) was performed on the second spot. As described above, a punch 6 mm in diameter was placed in 1.4 mL of PBS-BSA-TW and then incubated overnight at 4°C. The eluted volume was brought up to a total of 2 mL with the addition of a dilution buffer from the Western Blot kit and incubated with the strip. Subsequent steps were performed according to the manufacturer's recommendations.

All the results were validated by a medical biologist at the NRC and then recorded in the laboratory database.

Reporting to Participants

The reporting procedure was explained in the participant consent form and differed according to the results (positive or negative). If all 3 tests for HIV, HBV, and HCV proved negative, the NRC informed the participant and the GP by postal mail. However, in this correspondence, it was also indicated that tests conducted using DBS do not have the same performance levels as conventional screening methods based on plasma or serum collected on venous puncture performed by specialists and, consequently, are not as accurate. Participants were advised that in case of recent exposure at risk of infection, they should contact their GP for additional biological testing, if required.

When at least one of the tests was positive or showed a limit result, the NRC sent the results of all tests to the GP of that participant only (ie, not to the participant) under confidential cover, along with a letter informing the GP that the participant had been invited to obtain the results and advising the GP to verify the positive result using a conventional standard screening method. The NRC contacted the participant by postal mail inviting him or her to contact the GP designated in the consent form to obtain the results of all tests.

Reminders to Participants

Eight days after the self-sampling kit was posted to the participants, an email was automatically sent to those who had provided an email address, asking them to confirm reception or not. Those who did not receive the kit were invited to contact the survey institute for help and information.

The NRC sent a list of BaroTest identifier codes (reflecting individual participants) corresponding to the returned samples, twice a week to the survey institute by email. For each BaroTest ID listed, details were provided on what exactly had been received. In case of incomplete submissions (eg, no filter paper or no consent form) or missing information (eg, unsigned consent form or incomplete contact details), the survey institute telephoned the participant to enquire whether he or she required another sampling kit or consent form to be sent.

Participants were contacted by the survey institute if the DBS sample was not received by the NRC within 15 days after the self-sampling kit was sent. If the participant did not respond after 10 attempts, a voice message and email reminder (for those who had provided an email address) were sent. A second telephone reminder took place 10 days after the first one if no DBS reached the laboratory by that date. Similarly, a voice message was left after 10 attempts, and an email was sent if the person's email address was available.

Statistical Analyses

Number of Subjects Included and Number of Dried Blood Spots Expected

It was planned to include 15,000 people aged 15 to 75 years in the 2016 Health Barometer, approximately 14,000 of who were aged between 18 and 75 years.

The proportions of eligible individuals agreeing to participate in BaroTest and those who sent back the self-sampling kit were estimated on the basis of previous studies. In 2006, 76% of respondents in the French Sexual Behavior Survey agreed to receive a kit for the detection of Chlamydia trachomatis [19], and in a meta-analysis, Jamil et al calculated an average acceptance rate of 79% [20]. In the experiment described by Fisher et al [21], 62.5% of HIV-negative homosexuals seeking care in a medical setting accepted the proposed home self-sampling kits for sexually transmitted infection or HIV. Of these, 77.5% used them and returned their samples. In our BaroTest study, we assumed that half of the 14,000 eligible participants in the Health Barometer will agree to receive the kit for the BaroTest study. This percentage was lower than that observed in the studies mentioned above, as we considered the nature of the infection screened and the self-puncture used. Among the 7000 individuals who will receive the kit, we assumed that 70.00% (4900/7000) will return their DBS on filter paper, corresponding to 35% of the eligible Health Barometer participants. The 70.00% (4900/7000) return rate was based on the 68% and 62% participation rates in 2 French home-screening studies for chlamydia infections [19,22] and on the hope that our thorough system of reminders would maximize the rate of return.

As the highest expected prevalence was for the HBsAg, estimated at 0.65% in 2004, 5000 persons would make it possible to estimate this prevalence with an accuracy of approximately 0.22%.

Definitions and Assessment of Acceptability and Feasibility

Acceptability of this screening protocol was based on the percentage of eligible individuals agreeing to receive the self-sampling kit (acceptance rate), on the proportion of people returning the DBS (return rate), and on the proportion of participants out of the total eligible population.

The feasibility of self-sampling testing was based on the number of participants with adequately filled blood spots and the number of participants with blood spots for which at least one virological analysis could be performed.

The amount of blood received was assessed by the number and size of the blood spots. Spots were classified into 3 categories: (1) correctly filled, (2) incorrectly filled, and (3) empty blood spots. In a *correctly filled blood spot*, the spot was completely filled with approximately 10 µL of whole blood. An *incorrectly filled blood spot* was defined as either a blood spot with less than 10 µL of whole blood or an overfilled spot. An *empty blood spot* was defined as a completely empty blood spot.

Prevalence was defined as the proportion of persons testing positive among the population tested. These data were extrapolated to the general population considering the BaroTest participation rate and characteristics of the participants.

The proportion of infected persons unaware of their infection was defined as the proportion of people who reported either that they had never been previously screened or that their last test was negative in the Barometer, among those testing positive.

All indicators were analyzed according to the characteristics of the participants collected in the Health Barometer questionnaire:

- Sociodemographic characteristics: sex, age, country of birth, level of education, and employment status
- Past at-risk exposure to HIV, HBV, and HCV infection: transfusion; drug use; tattooing or piercing performed without single-use equipment; surgical, dental, or nursing care; or prolonged stays in high endemic areas (eg, Africa, Asia, or the Middle East)
- Awareness of hepatitis B and C and HIV serologic statuses: screening history and date and results of the last screening

The characteristics of those who refused to participate in the BaroTest and those who agreed to participate but did not return a biological sample were also analyzed.

Ethical Statements and Data Confidentiality

Information Provided to the Participant

The objectives and methods of the BaroTest study as well as the rights of participating individuals were presented both at the end of the telephone interview and in the letter of information sent with the self-sampling kit. At both times, the potential participant was informed that his or her participation was voluntary and that he or she was fully entitled to refuse participation with no prejudice of any kind. Moreover, mentioned in the letter of information was the right to object, to access, and to rectify participant information held electronically, in accordance with the provisions of Law Number 78-17, January 06, 1978 (French Data Protection Act).

Participant Consent

Consent to participate in the BaroTest was obtained at 2 points:

- Initial oral consent was obtained by telephone at the end of the Health Barometer interview after information was provided on the objectives of the study and guarantees given about of anonymity and confidentiality of the records.
- Written consent was obtained via the consent form sent with the self-sampling kit. On this form, it was explained that completed informed consent was required to be able to participate in the BaroTest and to be informed of the results. The right of opposition to, access to, and rectification of all data collected relating to the BaroTest was explained. Participants were advised to contact the survey institute in charge of managing the personal data files if they wished to exercise this right. Participants were also informed that the NRC would store completed consent forms for 15 years and then destroy them.

Reporting Screening Process

In accordance with the French law, the reporting process was dependent on the results of the tests (positive or negative, see above). To optimize reporting, several reminder procedures were implemented to minimize the risk that participants would return envelopes with missing or incomplete contact addresses. When returned consent forms only included clear contact details for the GP, screening results were sent to him or her with an explanatory letter. The GP was then responsible for sharing the results with the participant.

Confidentiality and Data Flow

For those who agreed to participate in the BaroTest, the survey institute was in charge of the recording of personal data at the end of the interviews as well as of sending the self-sampling kits and managing reminders.

To ensure the safety and confidentiality of personal data, a data file segregation procedure was implemented, whereby the matching of Health Barometer data (answers given during the phone questionnaire) with BaroTest data (testing results) was made impossible. Therefore, at no time did the survey institute receive or keep any of the results from the participants' tests. The NRC was in charge of managing personal contact data for the participants to ensure delivery of their test results. No transfer of personal data took place between the NRC and other partners (the survey institute, Santé publique France). NRC only sent the ID list of the BaroTest kits it received to the survey institute to manage reminders.

At the end of the study, Santé publique France received the following:

- From the survey institute: (1) an anonymized file of the answers to the Health Barometer 2016 questionnaire with Health Barometer identifiers and (2) a match list of BaroTest and Health Barometer IDs.
- From the NRC: (1) a file containing the BaroTest IDs, (2) the corresponding testing results, and (3) the following information: quality of DBS, date of self-sampling, date of receipt of the self-sampling envelope, GP contact information, and date the results sent by the NRC. This file did not include any personal data. Santé publique France was therefore in possession of 3 anonymized files that it merged using the BaroTest and Health Barometer identifiers to obtain a single database. Following the generation of this database, the BaroTest IDs were definitively deleted.

Timeline

Inclusion in BaroTest took place between January and July 2016. Following the reminder campaign and to account for late receipt of samples, it was decided that the NRC could analyze and report the results to the participants until December 31, 2016.

Results

The results on acceptability and feasibility of screening using home-based self-sampling are expected in the last quarter of 2018 and those on the prevalence estimates of HBV, HCV, and HIV infections in the first semester of 2019.

Discussion

The objectives of BaroTest were to assess the acceptability and feasibility of joint screening for HIV, HBV, and HCV infections using home self-sampling of capillary blood on filter paper and to both assess the number of persons affected in the general population and describe their characteristics.

The BaroTest was linked to a randomized telephone survey called the *Health Barometer*, which uses a complex call protocol

to increase the likelihood of interviewing hard-to-reach individuals and to achieve a high response rate. According to the current French bioethics law, the individuals without health insurance were unable to participate in the study, but their number was probably low. Indeed, in France, universal health coverage is accessible to low-income individuals or without any resources as well as the state medical aid for foreigners with an irregular administrative situation. In addition, it is uncertain that all participants with positive screening tests will consult the physician mentioned in their consent form to get their results. The main objective of this study was to target screening to enlarge the awareness of the serological status among the general population. We agree that it would have been efficient to link those tested positive to care. In fact, we proposed to the ethics committee that the medical staff of the NRC phone the participant when one of the tests was found positive. The participant could have been informed, counseled, and referred for control to a physician or the nearest screening center. However, the ethics committee refused this proposal because, in France, positive results have to be given by the GP to the patient face-to-face. That is why we sent the results (when one of the tests was positive) to the GP mentioned in the informed consent and informed the participant by mail that the results of the tests were available with the GP. We checked the address of the GP mentioned in the consent, but there was no mechanism to remind participants to contact their GP for results. However, results of studies on home sampling [23] and self-testing [24] showed that participants seem to base their follow-up behavior on the result of the test, and after an abnormal result, most of them seek medical care. We also assumed that most of the patients will be contacted by their physicians after receiving the positive results if they do not do so themselves. The whole reminder system was based on information feedback between the NRC and the logistic platform. Reminders were sent only to people who had not sent back their samples. For the results process, we were not in a position to have this feedback. To enhance this system and avoid this limitation, we have now succeeded in the advocacy of supporting the linkage to care with a specific telephone and email service, but those developments were not available in 2016 for BaroTest.

The Health Barometer was a real opportunity to experiment with a new screening approach for HIV, HCV, and HBV based on home self-sampling among a representative and large sample of the general population of mainland France (more than 14,000 participants). It also provides a reliable assessment and update of the burden of HBV, HCV, and HIV infections in the general population in France, while reducing the costs typically associated with this type of research. The Health Barometer questionnaire also provides a wealth of information on the opinions, knowledge, and practices of the population.

With respect to the methodology used in BaroTest (ie, telephone-based survey), the acceptance rate of home self-sampling was probably different than the rate one might expect, had the invitation to participate been made through other means, for example, via the internet. Nonetheless, the data from BaroTest will contribute to better profile potential users of the home self-sampling offer, in the context of reinforcement of screening policies.

Screening assays have slightly lower performance when DBS absorbed onto filter paper than using whole blood collected through venipuncture. However, meta-analyses showed that anti-HCV and HBsAg testing using DBS compared with venous blood sampling was associated with excellent diagnostic accuracy [25]. With the same techniques and thresholds used in the BaroTest, DBS specificity and sensitivity for anti-HCV detection have recently been estimated at 98.2% and 99.1%, respectively, with the corresponding estimated values for HCV RNA detection being 100% and 98.1% [26]. For HIV, DBS sensitivity to detect HIV-seroconversion is close to that of third-generation tests (antibody detection) performed under standard conditions [27]. Therefore, the risk of not accurately detecting HIV infection—even very recent infection—during the BaroTest survey would seem limited.

We will estimate the prevalence of chronic HBV and HCV infections and HIV infection according to the participation rate and characteristics of the participants. The BaroTest will also provide information on the proportions of people infected with HCV, HBV, or HIV who are unaware of their infection that is indispensable in the context of the development of new highly effective treatments to reduce morbidity and mortality. The BaroTest results will consequently help inform new strategies for HIV, hepatitis B, and hepatitis C screening and—if the acceptability and feasibility results of the study prove conclusive—will encourage the expansion of the current screening offer to include home self-sampling.

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Conflicts of Interest

None declared.

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Abbreviations

DAAs: direct-acting antivirals
DBS: dried blood spots
EIA: enzyme immunoassay
ELISA: enzyme-linked immunosorbent assay
GP: general practitioner
HBsAg: hepatitis B virus surface antigen
HBV: hepatitis B virus
HCV: hepatitis C virus
MSM: men who have sex with men
NRC: national reference center
PBA-BSA-TW: sodium phosphate buffer containing 10% bovine serum albumin and 0.05% Tween 20

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Protocol

Development and Management of Networks of Care at the End of Life (the REDCUIDA Intervention): Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: End-of-life needs can be only partly met by formalized health and palliative care resources. This creates the opportunity for the social support network of family and community to play a crucial role in this stage of life. Compassionate communities can be the missing piece to a complete care model at the end of life.

Objective: The main objective of this study is to evaluate the REDCUIDA (*Redes de Cuidados* or Network of Care) intervention for the development and management of networks of care around people with advanced disease or at the end of life.

Methods: The study is a 2-year nonrandomized controlled trial using 2 parallel groups. For the intervention group, we will combine palliative care treatment with a community promoter intervention, compared with a control group without intervention. Participants will be patients under a community palliative care team's supervision with and without intervention. The community promotor will deliver the intervention in 7 sessions at 2 levels: the patient and family level will identify unmet needs, and the community level will activate resources to develop social networks to satisfy patient and family needs. A sample size of 320 patients per group per 100,000 inhabitants will offer adequate information and will give the study 80% power to detect a 20% increase in unmet needs, decrease families' burden, improve families' satisfaction, and decrease the use of health system resources, the primary end point. Results will be based on patients' baseline and final analysis (after 7 weeks of the intervention). We will carry out descriptive analyses of variables related to patients' needs and of people involved in the social network. We will analyze pre- and postintervention data for each group, including measures of central tendency, confidence intervals for the 95% average, contingency tables, and a linear regression. For continuous variables, we will use Student *t* test to compare independent samples with normal distribution and Mann-Whitney *U* test for nonnormal distributions. For discrete variables, we will use Mann-Whitney *U* test. For dichotomous variables we will use Pearson chi-square test. All tests will be carried out with a significance level alpha=.05.

Results: Ethical approval for this study was given by the Clinical Research Committee of Andalusian Health Service, Spain (CI 1020-N-17), in June 2018. The community promoter has been identified, received an expert community-based palliative care course, and will start making contacts in the community and the palliative care teams involved in the research project.

Conclusions: The results of this study will provide evidence of the benefit of the REDCUIDA protocol on the development and assessment of networks of compassionate communities at the end of life. It will provide information about clinical and emotional improvements, satisfaction, proxy burden, and health care resource consumption regarding patients in palliative care.

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KEYWORDS

palliative care; public health; delivery of health care; community networks

Introduction

Palliative Care in the Community

Palliative care provides professional, scientific, and human responses to the needs of those living with advanced disease or facing the end of life, while also supporting their families [1]. Experts in this field are organized into multidisciplinary teams to provide a comprehensive care model to address suffering, symptom management, and other emotional, social, and spiritual aspects of the final stage of life, death itself, and the grief of relatives [2]. Palliative care is a type of care that best responds to the needs of these people and their families in such circumstances [3] and is internationally recognized as a right of citizens [4]. Palliative care can be provided across multiple settings. Studies indicate that, while aiming to be holistic, palliative care resources cannot possibly cover all patient and family needs [5]. Furthermore, differences in family structure mean that some patients might require more social and practical support than others. In these cases, mobilization of a person's wider support networks can play a crucial role [6].

The main family caregiver is recognized as the person most involved in the patient's care. This person, in Latin countries, usually is the contact with health and social care professionals and has to cope with the patient's daily physical, social, and emotional needs [7]. Outside of the immediate family network, other support networks can assume other necessary tasks [6]. Evidence suggests that up to 7 different profiles have been identified of people who participate in the care of someone facing a terminal illness [8]. Mobilization of this wider network is the base of compassionate communities [9].

Kellehear's theoretical framework of a compassionate community is gathering momentum internationally [10-12]. This new model of care operating in countries including the United Kingdom [13], Ireland [14], India [15], Canada [16], Australia [17,18], and Spain [19,20] brings together not only health and social professionals and primary caregivers but also the wider community (including extended family members, friends, neighbors, volunteers, and work colleagues) to support people and their families at the end of life. At a wider organizational level, the model of care may also include schools, universities, workplaces, companies, the arts community, social care and community development organizations, and policy makers [21]. It is intended that, through such a model of community intervention, there is an awakening and heightened activity of citizens regarding palliative and compassionate care [10-22]. Compassionate communities integrate and promote palliative care socially [23-25].

Health care organizations and policy makers are increasingly involved in the design, development, and evaluation of compassionate community models. It is recognized that they offer an opportunity to support the reconfiguration of health and social services, reduce costs, and facilitate models of integrated care [9]. The World Health Organization has included the development of compassionate communities based on awareness, training, and implementation of networks into their guide for the planning and implementation of palliative care services [26,27].

One of the largest and most successful models of compassionate communities in the world began in Seville, Spain. All with You [28] (a direct translation of the program's Spanish name, *Todos Contigo*) is a social innovation program created by the New Health Foundation in 2014 [19]. It seeks to transform care for people with advanced chronic conditions that require palliative care by monitoring and optimizing health care and social services, providing support to families, mobilizing community-based assets, and promoting greater awareness of the challenges and opportunities associated with palliative care and the management of complex chronic conditions.

To our knowledge, no protocol or tool is available to assess systematically these types of intervention, so it remains difficult to compare them and to assess their real effect.

As a part of the All with You program, the REDCUIDA (short for *Redes de Cuidados*, or Network of Care) intervention protocol has been developed. This protocol will offer a systematic method to assess the quality of the community intervention and its effect on clinical well-being, patient and family satisfaction, and consumption of health system resources.

Objective

The primary objective of this study is to evaluate the REDCUIDA intervention protocol for the creation and management of networks of care that cover the unmet needs of a person with advanced diseases or at the end of life.

The secondary objectives are to (1) identify the precise nature of a patient's unmet needs by palliative care teams that can be addressed through mobilization of the community, (2) detect members of the support networks that can meet the patient's identified needs and describe their fundamental characteristics (caregiver profiles), (3) analyze the influence of a community promoter's interventions on the emergence and growth of support networks as the disease progresses, (4) assess whether the REDCUIDA intervention improves the patient's quality of life and decreases the main caregiver's burden, (5) establish whether this intervention reduces professionals' workload and

health and social resource consumption during end-of-life care, and (6) analyze the influence of the REDCUIDA intervention on the preference of the place of care and death.

Hypothesis

We hypothesize that the use of the REDCUIDA protocol in a community intervention program allows for the expansion of care networks that can meet the needs and improve the quality of life of patients, increase family satisfaction, reduce the burden on main caregivers, improve the possibilities of care and death in the preferred place, and reduce the consumption of health care and social care resources during the end of life.

Methods

Trial Design

The study is a 2-year nonrandomized controlled trial using a 2-arm parallel group design conducted in the community. For the intervention group, we will combine the standard palliative care treatment with a community promoter's intervention; the control group will benefit from standard palliative care.

Intervention and control group participants will be patients under the community palliative care team's supervision living in 2 areas with and without community promoter intervention.

Setting

The study will be developed in the community, in 2 different geographic areas in Seville, Spain. The main difference between them will be the presence of a community promoter as a part of a new city program called All with You [19].

Eligibility Criteria

Inclusion criteria are patients living in Seville, with any advanced or terminal illness and receiving palliative care supervision, and having any of the following conditions: (1) total or serious dependence for basic and instrumental daily activities (Barthel Activities of Daily Living Index score <40; Lawton and Brody Instrumental Activities of Daily Living Scale score <3), (2) more than 40% of their needs not covered by the community, (3) a high score in loneliness on the Scale of Social Loneliness (ESTE) II (score >20 points), (4) having a person (family member, friend, neighbor, social worker, or other person) who acts as a communicator and principal person for support and is prepared and able to participate in the development of the network of care and share information with the community promoter, (5) having a main caregiver with an intense physical or emotional burden (scoring >56 on the Zarit Scale), and (6) accepting of the support and guidance by the community promoter with informed consent.

Exclusion criteria are patients who are in a very advanced terminal stage with life expectancy less than 1 week; those who do not have a high level of dependency and have their needs met by their family and other members of the community; and those who do not wish to participate.

Recruitment Procedure

Potential participants will receive information from palliative care team members. Reasons for declining to participate will be recorded as not interested, too busy, don't believe in it, and other.

Palliative care teams will arrange an appointment with the patient for the baseline assessment. This first appointment will take place in the patient's home. At this appointment, written informed consent for participation in the study will be obtained from participants.

Patients assigned to the intervention group will be those living in the San Pablo-Santa Justa area, Seville (60,000 inhabitants), who accepted the community promoter intervention. Patients assigned to the control group will be those living in an area with no community promoter available.

Intervention

We will deliver the REDCUIDA intervention over the course of 7 weeks (Figure 1). Different interventions will take place each week during a face-to-face meeting between the community promoter and the person living with advanced illness, or their families, or both.

We will conduct an initial (V0) assessment of the sociodemographic data of the beneficiary and his or her needs. This first step aims to detect the degree of care and support networks that could be mobilized during the progression of the disease. At this point, the community promoter will complete the beneficiary's referral sheet (Multimedia Appendix 1) and the requirements sheet (Multimedia Appendix 2 [29]). If more detailed information will be needed, a face-to-face meeting will be held with the health professional involved.

Following V0, we will determine the needs of care networks and interventions. Then, we will arrange a meeting among the beneficiary and his or her family, health care professionals, and the community promoter to inform all of them about creating and managing a specific caring network within their community (V1). This first visit will be used to understand the starting point as a baseline analysis for the activities ahead.

During the subsequent interventions, we will conduct several assessments (Table 1) based on the following scales. We will use the Barthel Index [29], in the original or a validated Spanish version [30], to identify needs related to basic daily living activities. This assessment can be self-administered, evaluated with direct observation, or completed by the patient or caregivers (Multimedia Appendix 2). We will use Lawton and Brody's original scale [31] to identify needs for instrumental daily living activities. This assessment can be self-administered, directly observed, or completed by the patient or caregivers (Multimedia Appendix 2).

Figure 1. Action procedures for the REDCUIDA protocol.

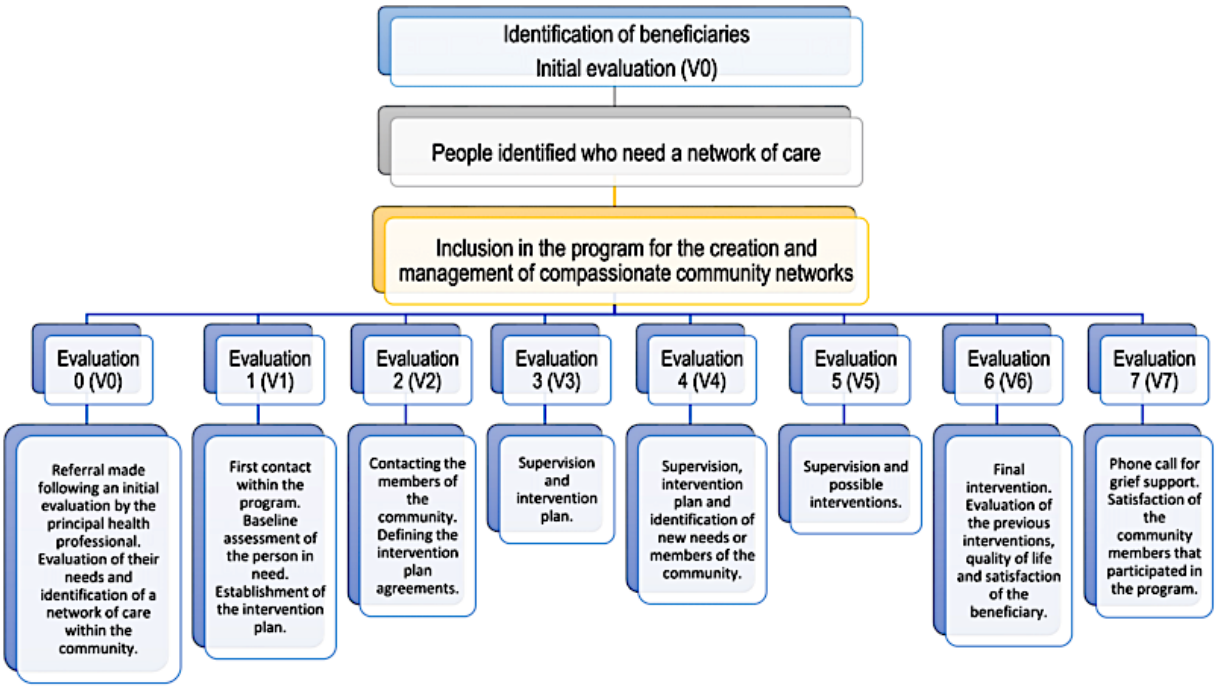

Table 1. REDCUIDA protocol for applying assessments to the beneficiary and the networks of care.

Assessment	Evaluation step							
	V0	V1	V2	V3	V4	V5	V6	V7
Inclusion and referral sheet	Yes	—	—	—	—	—	—	—
Networks of care	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—
Barthel Index	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—
Lawton and Brody scale	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—
Loneliness scale	Yes	—	—	—	—	—	Yes	—
Zarit Scale	Yes	—	—	—	—	—	Yes	—
EQ-5D-3L[a]	—	—	—	—	—	—	Yes	—
Family and network of care satisfaction	—	—	—	—	—	—	—	Yes

[a]EQ-5D-3L: 3-level EuroQol 5 dimensions questionnaire.

We have adapted Abel and colleagues' circles of care (Multimedia Appendix 3) [6], which can be self-administered or assessed via a direct interview with the patient or their caregivers. We will detect social solitude using the expanded ESTE II Scale [32] adapted from De Jong Gierveld and Van Tilburg [33], which must be administered directly to the patient or by the caregiver (Multimedia Appendix 4). We will use the 3-level EuroQol 5 dimensions questionnaire (EQ-5D-3L) [34] to asses quality of life. This descriptive system contains 5 dimensions of health (mobility, personal care, daily activities, pain and discomfort, and anxiety and depression), and each has 3 levels of severity (no problems, some problems or moderate problems, and serious problems). This assessment is self-administered or completed directly by the patient (Multimedia Appendix 5). We will use the Zarit Scale [35,36] adapted into Spanish [37] to assess the variable burden of the caregiver in the provision of care to chronically ill patients, which is administered by directly interviewing the caregiver (Multimedia Appendix 6). The Satisfaction Scale, adapted from Villavicencio et al [38] and Molina et al [39] (Multimedia Appendix 7), will be conducted by an external professional by phone on completion of the interventions.

During the intervention processes and the creation of networks of care, the community promoter will follow a series of activities based on Horsfall and colleagues' method for the creation of ecosystems of care around people at the end of life [40].

At the end of the interventions, a final evaluation (V7) will be conducted to reevaluate the needs coverage by the network and to evaluate family and caregivers' satisfaction. This phone questionnaire will be administered by an independent professional to avoid information bias.

Variables

The variables we will use for the descriptive study on the REDCUIDA protocol are the following: for patients' clinical and sociodemographic data: age, sex, and diagnosis; for families' sociodemographic data: age, sex, and relationship to the patient; for network of care profiles: relationship to the patient, age, and sex; number of needs according to Barthel Index and the Lawton and Brody scale; number of members of the care network; number of needs covered by the network; quality of life according to the quality of life scale EQ-5D-3L; degree of loneliness according to ESTE II Scale; burden of the principal caregiver according to the Zarit Scale; satisfaction regarding the care network according to the Satisfaction Scale; and place of death.

For community promoter activity data, we will determine the number of interventions performed at home and number of interventions carried out in the community (eg, district, neighborhood, city, community of neighbors).

To assess health care system resources, we will determine the number of hospital admissions in the last month; days of hospital stays in the last month; number of emergency visits in the last month; number of visits of the palliative care team to the home; number of visits of the palliative care team to a hospital; and number of telephone calls made by the palliative care team.

Sample Size Calculation

We have calculated a sample size of 320 patients per group for a population of 100,000 inhabitants based on the number of people dying of cancer each year (7000 people per million inhabitants) and the number of people in the final stage of nononcologic illnesses (approximately 4500 cases per million inhabitant). In a population of about 700 people, per year, 65% will require specialized palliative care (455 patients eligible for the study [41]).

We have considered that 30% of patients will not sign the informed consent forms or will not meet all the inclusion and exclusion criteria.

Sources of Information and Data Collection

We will collect data from the patient's own medical history and the information from the REDCUIDA protocol.

Data regarding variables not included in the protocol, such as the use of the health care system, will be collected through a direct interview with the patient or caregiver and the principal health care professionals regarding visits in the last month (Multimedia Appendix 8). In addition, we will ask palliative care professionals for these data (before and at the end of the care process).

The community promoter and health care professionals will have access to the beneficiary's clinical information once enrolled in a palliative care program. The permission of the beneficiary and their main caregiver or closest connection shall be required in writing and verbally in order to be able to access the data and use the corresponding data of the interventions for analytical purposes. To ensure confidentiality, the beneficiary's identification data will be coded so that they can't be identified by their clinical information.

The deidentified data will be returned to the community promoter and the New Health Foundation for data processing and analysis. The questionnaires will be coded with an alphanumeric identifier in a separate database independent of that containing the participant's identification data.

Statistical Methods

We will carry out an initial descriptive analysis of variables related to patients' needs and the profiles of people involved in the social network by degree of kinship.

We will analyze pre- and postintervention data for each group. These will include measures of central tendency (mean), confidence intervals for the 95% average, contingency tables (frequencies), and a linear regression.

To compare the groups, we will compare means. For continuous variables, we will use Student *t* test to compare independent samples with normal distribution and Mann-Whitney *U* test for nonnormal distributions. For discrete variables, we will use Mann-Whitney *U* test. For dichotomous variables (comparison of proportions), we will use Pearson chi-square test. All tests will be carried out with a significance level alpha=.05.

Ethical Considerations

Ethical approval for this study was given by the Clinical Research Committee of Andalusian Health Service, Spain (CI 1020-N-17), in June 2018. The study uses informed consent sheets approved by the Clinical Research Committee of Andalusian Health Service, Spain. The right to guarantee data protection will be fulfilled.

Results

This is a 2-year nonrandomized trial. The protocol has been approved by the Clinical Research Committee of Andalusian Health Service. The community promoter has been identified and has received an expert community-based palliative care course (550 hours). The community promoter will start making contacts in the community and the palliative care teams involved in the research project.

Discussion

Beneficiary Population

Results from this study would be applicable among a vast population, including palliative care patients in developing countries. It is known that 7000 people per million population globally die each year, 2500 per million die of cancer, and approximately 4500 per million die in the final stage of any nononcologic illnesses [41]. It is estimated that 65% of this population will need specialized palliative care.

If our results confirm that community social networks improve patients' and families' satisfaction at the end of life and correlates with the best use of health system resources, new palliative care systems may be developed.

Possible Limitations of the Study

As it is not a randomized clinical trial, some selection bias could be considered. If the protocol offers positive results, further randomized investigations will be warranted.

It could be difficult to achieve a clear conclusion if the intervention and control group results are very different, although our results from the descriptive analysis of the intervention group will provide relevant information.

We acknowledge that other clinical or psychosocial variables not included in this protocol can influence patients' needs and satisfaction. We have chosen basic variables that are recorded in the patient's medical history and are part of the palliative care approach. Depending on the results, we will consider modifying them for future studies in this line of research.

Conclusions

This is, to our knowledge, one of the first trials to measure the effectiveness of a nonprofessional network intervention on patient and family satisfaction, family burden, and use of heath resources.

The results of this study may provide some directions for future palliative care interventions at the community level with frail populations. These interventions may also provide a basis for training health professionals and social resources to improve patient–professional communication about end-of-life care for patients at home and stimulate the development of systematic palliative care community networks for this population.

Conflicts of Interest

None declared.

Multimedia Appendix 1

REDCUIDA protocol: inclusion and referral of the beneficiary.

[PDF File (Adobe PDF File), 50KB - resprot_v7i10e10515_app1.pdf]

Multimedia Appendix 2

REDCUIDA protocol: beneficiary's scale of needs (adapted from Mahoney and Barthel [29]).

[PDF File (Adobe PDF File), 51KB - resprot_v7i10e10515_app2.pdf]

Multimedia Appendix 3

Circle of the community network.

[PDF File (Adobe PDF File), 33KB - resprot_v7i10e10515_app3.pdf]

Multimedia Appendix 4

ESTE II Loneliness Scale.

[PDF File (Adobe PDF File), 35KB - resprot_v7i10e10515_app4.pdf]

Multimedia Appendix 5

EQ-5D-3L quality-of-life scale.

[PDF File (Adobe PDF File), 27KB - resprot_v7i10e10515_app5.pdf]

Multimedia Appendix 6

Zarit Scale for caregiver burden.

[PDF File (Adobe PDF File), 24KB - resprot_v7i10e10515_app6.pdf]

Multimedia Appendix 7

Family and social support network scale of satisfaction.

[PDF File (Adobe PDF File), 25KB - resprot_v7i10e10515_app7.pdf]

Multimedia Appendix 8

Questionnaire on use of the health care system.

[PDF File (Adobe PDF File), 194KB - resprot_v7i10e10515_app8.pdf]

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Abbreviations

EQ-5D-3L: 3-level EuroQol 5 dimensions questionnaire
ESTE II: Scale of Social Loneliness II
REDCUIDA: *Redes de Cuidados* (Network of Care)

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Protocol

The Clinical and Cost-Effectiveness of 4 Enzyme-Linked Immunosorbent Assay Kits for Monitoring Infliximab in Crohn Disease Patients: Protocol for a Validation Study

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Abstract

Background: Currently, treatment decisions for people with Crohn disease are based on clinical judgment and trial and error. Consequently, people may continue to receive high drug dosages and experience unnecessary toxicity when it is possible to reduce or discontinue without a detrimental effect on clinical outcomes. Therapeutic drug monitoring (TDM) involves regularly testing blood samples for drug and antibody levels that could help clinicians identify the optimal treatment strategy and pre-empt treatment failure. However, heterogeneity in the assays can lead to a discrepancy in results and difficulties in decision-making. Standardization of the kits, and therefore results, would allow clinicians to optimize the use of biologics. Currently, there is also a lack of evidence for the cost-effectiveness of TDM using commercial test kits.

Objective: This study aims to analyze the clinical and cost-effectiveness of 4 commercial enzyme-linked immunosorbent assay (ELISA) kits (LISA TRACKER, IDKmonitor, Promonitor, and RIDASCREEN) to generate evidence which could support a recommendation for wider adoption in the National Health Service.

Methods: We propose to carry out a prospective-retrospective predictive biomarker validation study using the blood samples and clinical/utilization data collected during the ongoing SPARE trial (NCT02177071). A total of 200 stored samples from people with Crohn's disease who respond to treatment with infliximab will be used along with clinical and cost data from the trial. We will investigate the relationship between the drug and antidrug antibody levels with the main clinical outcomes (relapse rate at 2 years and time spent in remission), as well as resource utilization and quality of life.

Results: Funding is being sought to conduct this research.

Conclusions: This is the first study to compare the 4 ELISA kits for monitoring infliximab in patients with Crohn disease. It aims to address the uncertainties in the potential benefits of using the technologies for TDM.

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KEYWORDS

antidrug antibodies; anti-TNF; Crohn’s disease; ELISA; inflammatory bowel disease; infliximab; therapeutic drug monitoring

Introduction

Background

Crohn disease and ulcerative colitis are the main conditions described as inflammatory bowel disease. Crohn disease is a chronic, fluctuating inflammatory condition of the digestive tract that can affect both adults and children. The main symptoms include chronic or nocturnal diarrhea, abdominal pain, rectal bleeding, and weight loss. The disease follows an unpredictable relapse (active disease) and remission (no symptoms) course with significant variation in the pattern and complexity of symptoms. During a relapse, patients often suffer substantial morbidity and require intensive treatment, including invasive investigations, costly drugs, and surgery. The prevalence of inflammatory bowel disease in the United Kingdom (UK) is estimated to be 240,000 with Crohn disease affecting about 115,000 people [1]. In 2006, the cost of inflammatory bowel disease to the National Health Service (NHS) was estimated at £720 million, based on the prevalence and an average cost of £3,000 per patient per year [2]. The cost today is likely to be significantly higher with the availability of new biological therapies that have an average annual cost per patient estimated between £10,000 and £15,000 [3]. At Guy's and St Thomas' NHS Foundation Trust, the Inflammatory Bowel Disease Service has approximately 600 patients receiving biological therapies incurring costs of £6 million per year.

Currently, there is no cure for this lifelong condition. Drugs are used to suppress the overactive immune system in people with Crohn disease, with the intention of inducing and maintaining remission. However, 30% of patients fail to respond to first-line drugs and will then be considered for anti-tumor necrosis factor (TNF) alpha biological therapies, such as infliximab (IFX) and adalimumab (ADAL). Anti-TNF alpha treatment aims to induce remission and prevent relapse by targeting the inflammation-causing protein, TNF alpha, rather than suppressing the immune system as a whole. Despite this, loss of response and relapse are common. The annual risk of loss of response is estimated at 13% per patient [4]. The typical response to loss of response is dose intensification; however, the underlying cause of the loss of response is not fully understood. The main hypothesis is that some patients develop antibodies against the biologics preventing the concentrations of the drug in the patient's bloodstream from reaching levels required to maintain remission. People whose disease responds to a TNF alpha inhibitor may continue receiving the same level of the drug even when it may be possible (or even beneficial [5]) to reduce the dose or withdraw the drug entirely without any detrimental effect on clinical outcomes. This continued treatment may lead to people experiencing unnecessary side effects. Treatment decisions for people with Crohn disease are based on clinical judgment and trial and error. Measuring the levels of TNF alpha inhibitors and associated antibodies in the blood could help clinicians to identify the best treatment strategy for a person with Crohn disease. This is known as therapeutic drug monitoring (TDM).

Numerous commercial kits are available for TDM of biologics for Crohn disease. The literature is inconclusive on whether enzyme-linked immunosorbent assay (ELISA) testing improves patient outcomes or is cost-effective [6-10], as they are not routinely used to optimize treatment. The optimal approach and frequency of delivering TDM are also uncertain. In a study of health care professionals' routine practice, only 45% reported using TDM during maintenance therapy for patients in remission [11]. One reason for this being heterogeneity in the assays which can lead to a discrepancy in results. Standardization of the kits, and therefore results, would allow clinicians to optimize the use of biologics.

In 2016, the National Institute for Health and Care Excellence (NICE) published diagnostics guidance on TDM of TNF alpha inhibitors (IFX and ADAL) in Crohn disease (referred to as DG22) [12]. DG22 evaluated the clinical and cost-effectiveness of 3 ELISA kits. The 3 commercial kits were (1) LISA TRACKER (Theradiag, Croissy-Beaubourg, France), (2) Immundiagnostik/BioHit Healthcare, Bensheim, Germany, and (3) Promonitor (Grifols Diagnostic Solutions, Emeryville, United States). They were considered for testing levels of TNF alpha inhibitors and antidrug antibodies in 2 populations: (1) people with Crohn disease whose disease responds to treatment with TNF alpha inhibitors and (2) those who experience secondary loss of response. The DG22 found many limitations within the evidence identified. No studies were found to be assessing direct clinical outcomes for any of the commercially available test kits, and there was a paucity of evidence on cost-effectiveness in general. The DG22 concluded that although the kits show promise, there is insufficient evidence to recommend routine adoption across the NHS.

In response to the uncertainties identified in DG22, NICE recommended future research focus on addressing gaps in the current evidence and investigating the potential benefits of using ELISA kits for Crohn disease treatment monitoring within the NHS. In May 2016, NICE requested King's Technology Evaluation Centre (KiTEC), based at King's College London, to plan and obtain funding for research that will address the uncertainties mentioned above. As part of this research, KiTEC will carry out a prospective-retrospective predictive biomarker validation study to assess the clinical and cost-effectiveness of the ELISA kits. This study will use the stored samples and the clinical and cost data from a multicenter, international randomized controlled trial "Prospective Randomized Controlled Trial Comparing Infliximab-Antimetabolites Combination Therapy to Antimetabolites Monotherapy and Infliximab Monotherapy in Crohn's Disease Patients in Sustained Steroid-Free Remission on Combination Therapy" (SPARE) NCT02177071. Results from this study would provide further impetus for the remaining NICE research recommendations:

- Assess the analytical and clinical validity of the tests and develop standardized primary reference standards
- Prospectively evaluate the clinical utility of the ELISA kits in people with Crohn disease who are losing responsiveness to infliximab

The SPARE Clinical Trial

One of the treatment strategies used in the management of severe active Crohn disease that has not responded to conventional therapy is combination therapy. In this approach, an

immunosuppressant drug (also known as an antimetabolite) such as azathioprine, mercaptopurine or methotrexate and an anti-TNF alpha agent called infliximab are used together. This combination is highly effective in inducing remission. The multinational "Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease" (SONIC) trial NCT00094458 (Europe, Israel, and North America) [13] demonstrated that infliximab plus azathioprine combination therapy was superior to infliximab monotherapy and azathioprine monotherapy to achieve steroid-free remission and mucosal healing in antimetabolites-naïve steroid-dependent or steroid-refractory patients.

Despite this superiority, maintaining such combination therapy long-term may generate cost and safety issues. The NICE and Scottish Medicines Consortium [14] mandate reassessment of patients on combination therapy at 12 monthly intervals with consideration of drug withdrawal where patients are in sustained deep remission.

However, there is currently insufficient data on relapse and recapture rates to inform such decision making [15-18]. In response to the lack of evidence, a prospective open-label, international 3-arm trial SPARE was launched in October 2015. This trial assessed the benefits of the continuation of combination therapy and the feasibility of infliximab or antimetabolites discontinuation in patients in sustained steroid-free remission after prolonged treatment with a combination of infliximab and antimetabolites. The purpose of the SPARE study, therefore, is to find the safest and most effective way for patients to discontinue their combination therapy by comparing 3 different withdrawal strategies:

- Continued combination therapy (immunosuppressant drug and infliximab)
- Immunosuppressant drug alone (so infliximab discontinued)
- Infliximab alone (so immunosuppressant discontinued)

This will help find out which strategy has the best chance of maintaining remission of Crohn disease and to determine the risk factors for (1) disease flare, (2) side effects, (3) quality of life, and (4) the impact on people's social and professional life. The aim is to be able to identify which patients for whom discontinuation of immunosuppressant drug or infliximab could be considered after 1 year of treatment and what would be the best treatment strategy. The SPARE trial has a planned duration of 2 years main study plus 2 years follow-up. The main coprimary outcomes are (1) clinical relapse rate at 2 years and (2) mean remission duration within 2 years. Secondary outcomes include (1) time to relapse in each arm, (2) treatment failure rate, (3) time to treatment failure, and (4) tissue damage progression. The estimated completion date is January 2020.

Other Relevant Clinical Trials

There are many additional ongoing or recently completed trials which fulfill the requirements of our validation study and could be contacted to obtain samples. Three trials were identified, 2 have taken place in Europe and 1 in America. All include populations with luminal Crohn disease treated with infliximab who have been in remission for at least 6 months (Textbox 1).

Study Objectives

The primary objective of this study is to validate the ELISA kits by examining the relationship between infliximab and antiinfliximab antibody levels measured in duplicate. These will be compared with the main clinical outcomes (relapse rate at 2 years and mean restricted time spent in remission). The secondary objective is to evaluate the effect of monitoring infliximab and antidrug antibody concentrations in serum samples on resource utilization and health-related quality of life in patients with Crohn disease who respond to treatment with infliximab.

Textbox 1. Three other relevant clinical trials.

1. **"Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab" (NOR-SWITCH)**
   - Total of 155 adult patients with Crohn disease were recruited in Norway
   - Blood samples were collected and stored in a biobank [19]
   - Completed in 2017
   - NCT02148640
2. **"Precision Dosing of Infliximab Versus Conventional Dosing of Infliximab" (Precision IFX)**
   - Currently recruiting 800 adult and pediatric patients with Crohn disease or ulcerative colitis in the United States who are in remission
   - Expected to be completed in December 2018
   - NCT02624037
3. **"GIS-SUSANTI-TNF-2015" (Anti-TNF Discontinuation)**
   - Currently recruiting 300 adult participants with ulcerative colitis or Crohn disease in Spain
   - Primary completion date is December 2020
   - NCT02994836

Methods

Interventions

Commercial laboratories have developed various assay procedures for TNF alpha inhibitors and antibodies against TNF alpha inhibitors. The LISA TRACKER (Theradiag, Croissy-Beaubourg, France), (Immundiagnostik/BioHit Healthcare, Bensheim, Germany), Promonitor (Grifols Diagnostic Solutions, Emeryville, United States) and RIDASCREEN (R-Biopharm, Darmstadt, Germany) are particular examples of these essays classed as solid-phase ELISAs. They are intended to be used for measuring the levels of TNF alpha inhibitors and antibodies against TNF alpha inhibitors in the blood of people having treatment with biologics for Crohn disease. However, these kits vary in designs and there is a lack of standardization. Their unique features are detailed in the following (see Tables 1 and 2).

Study Population

The study population is patients who have been in steroid-free remission for at least 6 months undergoing infliximab/antimetabolites combination therapy scheduled for at least 1 year. The population must also have had infliximab treatment administrated every 8 weeks for the last 6 months. Detailed inclusion and exclusion criteria are presented below (Textbox 2).

Table 1. Drug assay kit specifications.

Details	Drug assay			
	IDKmonitor	LISA TRACKER (Infliximab)	Promonitor (Infliximab)	RIDASCREEN
Microplate coating	Anti-IFX[a] monoclonal antibody	Recombinant TNF[b] alpha	Anti-TNF alpha monoclonal antibody bound to recombinant TNF alpha	TNF alpha
Primary conjugate	HRP[c]-conjugated anti-IFX monoclonal antibody	Biotinylated antihuman IgG1[d] antibody	HRP-conjugated anti-IFX monoclonal antibody	HRP-conjugated anti-IFX monoclonal antibody
Secondary conjugate	—[e]	Streptavidin-HRP conjugate	—	—
Detection method	TMB[f]	TMB	TMB	TMB
Measurement range (µg/mL)	0.4-45.0	0.3-16.0	0.035-14.4	0.1-12.0[g]

[a]IFX: infliximab.

[b]TNF: tumor necrosis factor.

[c]HRP: horseradish peroxidase.

[d]IgG1: immunoglobulin G subclass 1.

[e]TMB: tetramethylbenzidine

[f]Not applicable.

[g](2.0-48.0 on dilution).

Table 2. Antidrug antibody assay kit specifications.

Details	Antidrug antibody assay			
	IDKmonitor (total)[a]	LISA TRACKER (free)	Promonitor (free)	RIDASCREEN (free)
Microplate coating	Streptavidin	IFX[b]	IFX	IFX
Primary conjugate	HRP[c]-conjugated IFX	Biotinylated-IFX	HRP-labelled IFX	Biotinylated-IFX
Secondary conjugate	Biotinylated-IFX	Streptavidin-HRP conjugate	—[d]	Streptavidin-HRP conjugate
Detection antibody	TMB[e]	TMB	TMB	TMB
Measurement range	10 arbitrary unit/mL[f]	10-200 ng/mL	2-1440 arbitrary unit/mL	2.5-125 ng/mL[g]

[a]Samples are subjected to manual infliximab-antidrug antibody dissociation step.

[b]IFX: infliximab

[c]HRP: horseradish peroxidase

[d]Not applicable.

[e]TMB: tetramethylbenzidine.

[f]Semiquantitative, single cutoff.

[g](20-1000 ng/mL extended range).

Textbox 2. Study inclusion and exclusion criteria.

Inclusion criteria

- Diagnosis of luminal Crohn disease
- Male or female, ≥18 years of age to ensure data is comparable with other participating regions
- Currently treated using a combination therapy of infliximab and antimetabolites for luminal Crohn disease
- Combined therapy with scheduled infliximab and antimetabolites for at least 12 months
- Scheduled administration of infliximab 5 mg/kg every 8 weeks over the last 6 months
- Antimetabolites administered at a stable dosage for the last 6 months (ie, at least 1 mg/kg or 2 mg/kg for mercaptopurine and azathioprine, respectively, or the highest tolerated dosage if intolerance to standard dose and at least 15 mg/week subcutaneously for methotrexate)
- Patients in steroid-free clinical remission for at least 6 months according to the retrospective assessment of the patients' files
- Crohn's Disease Activity Index <150 at baseline
- Adequate contraceptive (as judged by the principal investigator) during the whole study for female participants of childbearing potential
- Patients able to understand the information provided to them and to give written informed consent for the study

- Patients who have presented a severe acute or delayed reaction to infliximab
- Perianal fistulae as the main indication for infliximab treatment
- Active perianal/abdominal fistulae at time of inclusion, defined by active drainage
- Patients with ostomy or ileoanal pouch
- Pregnancy or planned pregnancy during the study or breastfeeding
- Inability to follow study procedures as judged by the investigator
- Noncompliant subjects
- Participation in another therapeutic study
- Steroid use ≤6 months prior to screening
- Currently receiving steroids, immunosuppressive agents (other than purine, methotrexate), biologic treatment (other than infliximab) or thalidomide

The overall SPARE target is 300 randomized patients (100 per arm) worldwide over 20 months from 70 centers. Currently, the plan of recruitment is as follows:

- 100 patients in 20 centers (France)
- 70 patients in 21 centers (UK)
- 50 patients in 10 centers (Sweden)
- 45 patients in 10 centers (Germany)
- 35 patients in 9 centers (Belgium)

The KiTEC study will focus on 2 of the 3 study arms in which participants are being treated with infliximab. Participants from the other arm were excluded because they are not currently being treated with infliximab.

Study Design

The retrospective-prospective study will focus on patients with luminal Crohn disease who have sustained remission and are being treated with infliximab. Assays will be prospectively performed in duplicate on 200 blood serum samples. The samples were retrospectively collected from the SPARE trial. Our primary collaborator from the SPARE trial is Dr Edouard Louis (Centre Hospitalier Universitaire de Liège, Belgium), who is also the principal investigator.

The SPARE trial is an open-label, multicenter trial with 3 parallel randomized arms comparing 3 strategies of maintenance therapy in patients in sustained clinical remission without steroids for at least 6 months and having been treated by a combination of antimetabolites and infliximab for at least 1 year (Multimedia Appendix 1). Participants in study arms 1 and 3 who have sustained remission (referred to as "responders" and denoted as G2, G6, G8, and G12 in Multimedia Appendix 1) are the population focused on in this study. The SPARE trial is estimated to run for 5 years including 2 years of enrolment, 2 years of patient follow-up, and 1 year of data analysis. The trial began on October 2015 and has an estimated study completion date on January 2020. The KiTEC study is planned to last 18 months and overlap with the SPARE trial.

The blood samples will be sent to Viapath Analytics, the provider of pathology services at St Thomas' Hospital, for testing with the 4 ELISA kits under investigation. All ELISA kits will be automated on Dynex DS2 2-Plate ELISA processing system in accordance with the manufacturer's instructions for use. Sample analysis will be completed sequentially to avoid further freeze-thaw cycles. It is important to eliminate sources of variation that can be introduced due to repeated cycles. At the time point of analysis with each kit, all samples would have gone through the same treatment (ie, freeze-thaw cycles). Although measurement of uncertainty with each kit is known, drug/antidrug antibody complexes may show patient dependent variation upon freeze-thaw cycles and lead to further variation in different assay formats. This is accounted for by analysis of samples in identical integrity conditions. Pseudo-anonymized

results from the testing will be compared with the results from the SPARE trial to validate the kits. Stored samples will be prepared, stored, and shipped according to the SPARE lab manual. Serum samples will be centrifuged and frozen before shipping. All biological samples will be retained within the central labs (in Israel) at –80°C for at least 6 years. All SPARE trial data will be collected in an electronic case report form by staff at participating sites. The Trial Statistician, Professor Sylvie Chevet (Biostatistics and Medical Information Department, Saint-Louis Hospital) will perform data collection and data quality controls.

Statistical Analysis

All SPARE trial data are collected in an electronic case report form by staff at participating international sites. The data will be pseudo-anonymized. The Statistical Center in France will perform data collection and data quality control.

The coprimary outcomes are clinical relapse rate at 2 years and mean remission duration within 2 years. The following outcomes will also be assessed: (1) Inflammatory Bowel Disease Disability Index Scores, (2) Crohn Disease Activity Index, (3) adverse events, (4) trough levels of infliximab and fecal calprotectin, (5) direct and indirect costs associated with using or not using TDM, (6) health-related quality of life (EuroQol-5D and Short Health Scale), and (7) work productivity and activity index (Work Productivity and Activity Impairment Questionnaire in Crohn Disease).

Ethics

All serum samples analyzed will be obtained during the SPARE trial. The SPARE trial was conducted following the principles of the International Conference on Harmonization Good Clinical Practice. A research ethics board reviewed the SPARE trial at the respective site. All subject information used in this study was deidentified for the subject identification number and investigational site. The informed consent process complied with the International Conference on Harmonization Good Clinical Practice and all applicable regulatory requirement(s). The consent of subjects included the use of the collected data and serum for other medical purposes. Therefore, additional consent for the current study was not required.

Results

Funding has been sought to carry out this proposed research. This study is expected to take 18 months.

Discussion

Importance of the Study Results

The rationale behind conducting this study is to contribute to answering the questions identified by the research recommendations from DG22. If substantive evidence is generated, NICE will update its guidance to recommend the clinical use of one or more of the commercial ELISA kits for therapeutic monitoring and personalizing anti-TNF alpha inhibitor treatment. NICE guidance would encourage adoption both nationally and internationally, underpinning the potential value of this research. This technology has the potential to improve patient outcomes concerning clinical outcomes and patient-reported health-related quality of life. It also may be found to be cost effective. All of these are under investigation in our research.

Previous trials have found that varying infliximab in Crohn disease patients can have beneficial implications. One study, the “Stop Infliximab in Patients with Crohn's Disease” (STORI) trial (NCT00571337) [20] is an randomized controlled trial in France and Belgium which suggested that steroid-free remission may be maintained after infliximab discontinuation, with more than half of the 115 patients having reached sustained steroid-free remission after infliximab treatment with antimetabolites combination therapy for one to two years. This infliximab-free remission for a majority of the population will lead to substantial reductions in associated costs and side effects. This study also suggested that infliximab retreatment is safe and effective for relapsing patients. Further, in a 7-year follow-up, 21% of the population did not restart treatment with infliximab or another biologic [21]. However, the STORI trial did not have a control group of patients who were continuing infliximab treatment. Therefore, no results on when it is appropriate to recommend the withdrawal of infliximab from patients were discussed. The present study differs in that the population in focus is those continuing to use and respond to infliximab. Validating the technologies may lead to them being used clinically for informing treatment decisions and then, further clinical studies into the reduction or withdrawal of infliximab would be possible.

One advantage of utilizing the SPARE trial data for our research is that a quarter of the study population will be recruited from UK-based centers. This means that the cost data collected as part of the health economic analysis portion of our study will be directly relevant to treatment on the NHS. However, the circumstance of this study being an add-on to an international randomized controlled trial means we are highly dependent on the progress of that trial. Delays in the SPARE trial will impact on our progress and factors affecting recruitment numbers, or data quality will have a direct impact on our study. The samples obtained from the trial are to be retained for 6 years. Thus, it is highly likely we will be able to obtain the samples and conduct the validation study within this timeframe.

Conclusion and Future Direction

The proposed study will validate 4 commercially available ELISA test kits and potentially impact on a NICE recommendation for using the technology clinically. This research is directly answering one of the research recommendations from NICE to investigate clinical outcomes associated with using the ELISA kits for TDM in people with Crohn disease who respond to treatment with TNF alpha inhibitors. Future studies into evaluating the clinical and cost effectiveness of the technologies prospectively in an NHS clinical environment will be a key aim for further research.

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Authors' Contributions

TL led on writing the manuscript. KG, LK, ZA, PI, and MS were involved in developing the study protocol. All authors participated in the critical review of the methods and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

A flowchart of the SPARE clinical trial.

[PNG File, 399KB - 11218-218447-3-SP-png.png]

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Abbreviations

ADAL: adalimumab
ELISA: enzyme-linked immunosorbent assay
HRP: horseradish peroxidase
IFX: infliximab
IgG1: immunoglobulin G subclass 1
KiTEC: King’s Technology Evaluation Centre
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
SONIC: Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease
SPARE: Prospective Randomized Controlled Trial Comparing Infliximab-Antimetabolites Combination Therapy to Antimetabolites Monotherapy and Infliximab Monotherapy in Crohn's Disease Patients in Sustained Steroid-Free Remission on Combination Therapy
STORI: Stop Infliximab in Patients with Crohn's Disease
TDM: therapeutic drug monitoring
TNF: tumor necrosis factor
UK: United Kingdom

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Protocol

Unraveling the Biopsychosocial Factors of Fatigue and Sleep Problems After Traumatic Brain Injury: Protocol for a Multicenter Longitudinal Cohort Study

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Abstract

Background: Fatigue and sleep problems are common after a traumatic brain injury (TBI) and are experienced as highly distressing symptoms, playing a significant role in the recovery trajectory, and they can drastically impact the quality of life and societal participation of the patient and their family and friends. However, the etiology and development of these symptoms are still uncertain.

Objective: The aim of this study is to examine the development of fatigue and sleep problems following moderate to severe TBI and to explore the changes in underlying biological (pain, brain damage), psychological (emotional state), and social (support family, participation) factors across time.

Methods: This study is a longitudinal multicenter observational cohort study with 4 measurement points (3, 6, 12, and 18 months postinjury) including subjective questionnaires and cognitive tasks, preceded by 7 nights of actigraphy combined with a sleep diary. Recruitment of 137 moderate to severe TBI patients presenting at emergency and neurology departments or rehabilitation centers across the Netherlands is anticipated. The evolution of fatigue and sleep problems following TBI and their association with possible underlying biological (pain, brain damage), psychological (emotional state), and social (support family, participation) factors will be examined.

Results: Recruitment of participants for this longitudinal cohort study started in October 2017, and the enrollment of participants is ongoing. The first results are expected at the end of 2020.

Conclusions: To the authors' knowledge, this is the first study that examines the development of both post-TBI fatigue and sleep longitudinally within a biopsychosocial model in moderate to severe TBI using both subjective and objective measures. Identification of modifiable factors such as mood and psychosocial stressors may give direction to the development of interventions for fatigue and sleep problems post-TBI.

Trial Registration: Netherlands Trial Register NTR7162; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=7162 (Archived by WebCite at http://www.webcitation.org/6z3mvNLuy)

International Registered Report Identifier (IRRID): RR1-10.2196/11295

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KEYWORDS

traumatic brain injury; sleep; fatigue; biopsychosocial model

Introduction

Traumatic brain injury (TBI) is one of the most serious, disabling neurological disorders, with 10 million patients affected annually worldwide [1]. Consequently, societal costs are high and estimated to be around €33 billion in Europe [2]. TBIs appear on a spectrum of injury severity based on widely recognized injury characteristics. The more frequent mild TBIs are considered as trivial and benign injuries as opposed to less prevalent moderate to severe injuries, which are associated with long-lasting consequences for the patients and their environment [3]. Due to the high individual and societal costs associated with extensive rehabilitation needs and chronic disability, moderate to severe TBI represents a critical public health issue [4], with fatigue and sleep problems playing significant roles in the recovery process [5,6]. Between 30% and 70% of the patients experience fatigue [7], and a meta-analysis indicated that 53% experience sleep problems [8].

Study results concerning the presence of fatigue and type of sleep problems post-TBI are inconsistent, probably due to different study methodologies. Patients are included at different time points since their injuries and injury severity parameters differ across studies, measurement instruments are diverse, and there is limited consensus on what variables at which moment in time should be measured [9]. In addition, most studies are cross-sectional and not longitudinal in terms of design. This makes it difficult to compare results across studies and to draw conclusions about sleep and fatigue changes after TBI [10,11]. Nevertheless, post-TBI sleep problems and fatigue are often consistently experienced as the most severe and distressing symptoms [5], interfering with recovery and rehabilitation treatment and negatively impacting the quality of life [12]. Furthermore, despite the magnitude and impact of these phenomena, the etiology is still debated and no efficacious treatments have been established [13].

Recovery from moderate to severe TBI is a time-consuming and long-term process and should, therefore, be explained in terms of a disease process. Accordingly, different factors may be involved in fatigue and sleep problems at different stages after the injury [14,15]. By exploring the underlying causes of fatigue and sleep problems and how these symptoms develop over time, key periods may be identified in which specific targeted interventions are needed. The outcome and prognosis following TBI are extremely variable across individuals regardless of the severity of the initial injury [9], which implies that outcome is not only influenced by biological factors but should be studied in a biopsychosocial model in which physical, cognitive, affective, and social factors interact with sleep-wake patterns and fatigue [7,9,16,17]. Previous research has already shown the involvement of biological factors (eg, structural changes in the brain [18] and pain [19]) and psychological (eg, emotional distress [20,21]) and social components (eg, community integration and social support [22,23]) in fatigue and sleep problems following TBI. These factors are also involved in sleep and fatigue in other chronic diseases such as cancer, multiple sclerosis, and diabetes [24]. However, no studies, to the authors' knowledge, have yet examined these biopsychosocial factors in a comprehensive model over time to determine the significant underlying factors that contribute to post-TBI fatigue and sleep problems. Understanding these complex interactions is crucial to establish, explain, and treat fatigue and sleep problems associated with TBI. Therefore, this study proposes a biopsychosocial explanation of post-TBI fatigue and sleep problems.

The aim of the study is to examine the development of post-TBI fatigue and sleep problems longitudinally within a biopsychosocial model including several factors in moderate to severe TBI. The primary focus of the study will be on subjective fatigue and sleep problems post-TBI. We hypothesize that the associations between biopsychosocial factors and post-TBI fatigue and sleep problems change over time, that is, the associations with biological factors are strongest in the first 6 months and then decline, whereas the associations with psychological and social factors are initially weak but slowly increase and become apparent between 12 and 18 months. Previous research has shown a discrepancy between objective and subjective measures of fatigue and sleep in the TBI population [21,25]. Therefore, the secondary aim of the study is to examine the development of post-TBI fatigue and sleep problems with objective measures within a biopsychosocial model. In this paper, the design of the study will be presented.

Methods

Design

This study is a multicenter, observational, prospective longitudinal cohort study in which participants are followed using 5 assessments during the first 18 months following moderate to severe TBI. The Medical Ethics Committee of University Hospital Maastricht/Maastricht University (NL60322.068.17) and all participating centers approved the study protocol. The study is registered in the Dutch Trial Register (NTR67162, registered on April 10, 2018).

Study Population

Moderate to severe TBI patients are being recruited from emergency, neurology, and rehabilitation departments in several hospitals and rehabilitation clinics across the Netherlands. On the basis of a linear mixed regression analysis with a medium effect size (F_2=0.15), 7 significant predictors, a statistical power of 0.8, alpha level of .05, and a high test-retest reliability of at least 0.8 of the main study variables, the required sample is 103 TBI patients [26]. A dropout of 25% during the 18-month

follow-up is expected based on previous studies [27,28]. Therefore, 137 patients will be recruited to lead to a total of 103 TBI patients being available for the analyses.

Inclusion and Exclusion Criteria

TBI patients are eligible to participate in this study if they have a clinically confirmed diagnosis of a first moderate to severe, closed-head TBI, which is defined as Glasgow Coma Scale score<13 [29]; post-traumatic amnesia (PTA)>24 hours; trauma-related intracranial neuroimaging abnormalities; or loss of consciousness (LOC)>30 min [30]. In addition, participants must be aged between 21 and 70 years, fluent in Dutch, and provide informed consent.

Participants are excluded if they (1) had a prior moderate to severe TBI diagnosed by a neurologist or a mild concussion in the last half year; (2) have another condition that may interfere with the study outcome (eg, other pre-existing neurological disorder [stroke, brain tumor, etc], sleep-wake disturbance, fatigue due to any medical condition other than TBI, history of alcohol or drug abuse, prior mental disorder [for which treatment was necessary], or pregnancy); or (3) lack the ability to complete questionnaires based on clinical judgment (aphasia, severe cognitive impairment).

Participants meeting the following criteria are excluded during the study: (1) participant wants to leave the study or (2) there is a new incidence of TBI, other neurological disease/injury, or traumatic injury during the follow-up period.

Procedure

Patients are informed about the study by their treating physician (eg, neurologist, head nurse, or rehabilitation specialist). If the patient is interested in participating, a screening visit within the first 6 weeks after injury is done by the researcher, during which the informed consent is signed (if the patient is eligible and decides to participate). During this visit, demographics and preinjury characteristics are collected.

The follow-up appointments take place at approximately 3 months (V1), 6 months (V2), 12 months (V3), and 18 months (V4) postinjury, within 2 weeks before or after the exact follow-up date (ie, time window of 1 month). These visits consist of filling out questionnaires and performing cognitive tasks and can take place at Maastricht University, one of the participating clinical institutes, or the home of the participant. The visit will be guided by the researcher or a research assistant and are always scheduled between 11:00 am and 3:00 pm to minimize effects of the circadian rhythm [31]. In the week before these visits, the participant will wear an actigraph and fill out a sleep diary for 7 days at home (daily living). A reminder phone call is given at the start of the registration period, and during the 7 days, we will phone the participants twice to remind them. With the participant's permission, partners or family members of the participant are informed about the study to monitor whether the actigraph is worn. Participants receive 10 euros for each follow-up visit, and their travel expenses are reimbursed.

Measurements

The main outcomes are fatigue and sleep. The primary focus of this study is on subjective level of fatigue and sleep problems, affecting the quality of sleep, to address the experience of these problems by TBI patients. The relation over time between subjective fatigue and sleep and the biopsychosocial predictors shown in Table 1 will be examined. Second, the relation between objective fatigue and sleep measurements and the biopsychosocial predictors will be examined. An overview of all measurement instruments that are administered during the 18-month follow-up is shown in Table 1. The questionnaires are implemented in an online format, except for the demographic questionnaire, which is in an interview style. All questionnaires included in this study have good psychometric properties and have been used in the TBI population before.

Primary Outcome Measures

Subjective fatigue is measured with the Fatigue Severity Scale (FSS) [32]. The FSS is widely used, and it measures the impact of fatigue on activities of daily life and distress caused by fatigue; it includes 9 items related to fatigue, which are rated on a 7-point Likert scale. The mean score of the FSS is calculated and ranges from 1 to 7, where a higher score denotes more severe fatigue and a mean score of 4 or higher indicates severe fatigue [32]. The internal consistency is high [32], test-retest reliability is satisfactory, and the FSS can distinguish fatigue in brain-injured patients from that of controls [49].

Subjective sleep quality is assessed with the Pittsburgh Sleep Quality Index (PSQI) [33]. The PSQI consists of 19 items and examines 7 components, namely, overall sleep quality, sleep onset latency, total sleep time, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The global score is calculated by adding the 7 component scores and ranges from 0 to 21, where a lower score denotes better sleep quality. The questionnaire can discriminate between "good" and "poor" sleepers, with a global score of >5 indicating poor sleep quality [33]. The internal consistency and test-retest reliability of the PSQI are high, and the PSQI has good concurrent validity with sleep diary data [33]. The Dutch version of the PSQI has been used to examine sleep quality in acquired brain injury patients [50].

Predictors

The development of sleep and fatigue is examined with a biopsychosocial model. Therefore, the factors taken into account as predictors can be divided in biological (eg, structural changes in the brain and pain), psychological (eg, emotional distress and the burden of cognitive impairments), and social components (eg, community integration and social support).

Pain

The general level of pain is measured with a 100-mm visual analog scale [34]. The left end of the VAS represented "no pain" and the right end represented "most severe pain imaginable" with no intermediate divisions or descriptive terms [34]. The score ranges from 0 to 10, where a higher score indicates more severe pain. Pain intensity in the last 24 hours is measured. The VAS is widely used to measure pain in TBI patients [22], and it is suggested as a valid and reliable measure [51].

Table 1. Overview of all measurement instruments for the traumatic brain injury patients and the times of administration.

Parameter	Instrument	Screening (<6 weeks)	3 months	6 months	12 months	18 months
Main outcome parameters						
Subjective fatigue	Fatigue Severity Scale [32]	—	✓	✓	✓	✓
Subjective sleep quality	Pittsburgh Sleep Quality Index [33]	—	✓	✓	✓	✓
Predictors						
Pain (subjective)	Visual analogue scale pain [34]	—	✓	✓	✓	✓
Objective cognitive performance	Stroop, COWAT[a], digit span, SDMT[b] [35]	—	✓	✓	✓	✓
Physical activity	7 days actigraphy [36]	—	✓	✓	✓	✓
Emotional distress	Hospital anxiety and depression scale [37]	—	✓	✓	✓	✓
Cognitive complaints	Dysexecutive Questionnaire Revised [38]	—	✓	✓	✓	✓
Participation	Utrecht Scale for Evaluation and Rehabilitation-Participation [39]	—	✓	✓	✓	✓
Social support	Multidimensional Scale of Perceived Social Support [40]	—	✓	✓	✓	✓
Secondary outcome parameters						
Objective sleep wake disturbances	7-days actigraphy [41]	—	✓	✓	✓	✓
Objective fatigue	Psychomotor vigilance task [42]	—	✓	✓	✓	✓
Group characteristics and monitor the participants						
TBI characteristics	Injury severity such as structural imaging data, LOC[c], PTA[d], injury severity score; causes of injury; comorbid (physical) injuries, seizures; drug or alcohol intoxication during injury from the hospital database.	✓	—	—	—	—
Demographics	Age, gender, education, marital status, and work status	✓	—	—	—	—
Premorbid sleep	Premorbid question of PSQI[e] [33]	✓	—	—	—	—
Premorbid participation	Premorbid frequency and satisfaction of the USER-P[f] [39]	✓	—	—	—	—
Daytime sleepiness	Epworth Sleepiness Scale [43]	—	✓	✓	✓	✓
Multidimensional aspects of fatigue	Dutch Multi-Factor Fatigue Scale [44]	—	✓	✓	✓	✓
Subjective sleep-wake	7 days sleep diary [45]	—	✓	✓	✓	✓
Posttraumatic stress disorders	PTSD[g] checklist for DSM-5 [46]	—	—	✓	—	✓
Coping style	Proactive and passive coping scale of the Utrecht Coping List [47]	—	✓	—	—	✓
Drugs/alcohol/medication use	Demographic questionnaire	✓	✓	✓	✓	✓
Sleepiness preceding the task	Karolinska sleepiness scale [48]	—	✓	✓	✓	✓

[a]COWAT: controlled word association test.

[b]SDMT: symbol digit modalities test.

[c]LOC: loss of consciousness.

[d]PTA: posttraumatic amnesia.

[e]PSQI: Pittsburgh Sleep Quality Index.

[f]USER-P: Utrecht Scale for Evaluation and Rehabilitation-Participation.

[g]PTSD: posttraumatic stress disorder.

Cognition

A short test battery is used to assess cognitive performance. The extent to which cognitive functioning is affected is used as a proxy for the severity of the brain damage [52]. Cognitive tasks include measurements of speed, attention, interference, and executive functioning. The following 4 tasks are included, and the first 3 tasks are recommended as outcome measures in TBI research to measure neuropsychological impairments [35]:

1. *Stroop task* measures response interference control, a cognitive form of inhibition/flexibility and selective attention [53]. Previous studies showed inhibition deficits following TBI and a slower response time [54]. The stroop has good psychometric properties [35].
2. *Controlled oral word association test* (COWAT) [55] is a verbal fluency test, which measures the spontaneous production of words belonging to a specific category or a designated letter. This test measures attentional control, working memory, and other components of executive functioning. Focal frontal injuries following TBI show a strong association with performance on the COWAT [56]. COWAT is a reliable measure and is sensitive to TBI severity [57].
3. *Digit span* is a working memory task that assesses auditory attention. Both the forward and the backward order are used. The digit backward order is especially informative for working memory. This task has been used as a marker of cognitive deficit and recovery and has a high reliability [57].
4. *Symbol digit modalities test* (SDMT) is a cognitive test that measures attention and processing speed. The SDMT is sensitive to impairments of speed of information processing following TBI [58] and is a reliable measure [59].

Physical Activity

Daytime levels of physical activity are examined with actigraphy, which is a noninvasive method to monitor the rest/activity cycle [36]. In addition, actigraphy is used for the secondary aim regarding objective measures of sleep. The actigraph is a wristwatch-like device, worn on the nondominant wrist, which allows the participant to continue normal routines in the natural environment. There is no remote monitoring whether the actigraph is worn; however, the actigraph can be worn continuously during this week also when bathing. The actigraph (GENEActiv, Activinsights Ltd, Cambridgeshire, United Kingdom) measures the movement/motor activity of the participant, and thereby, the time spent in sedentary behavior, light intensity physical activity, moderate to vigorous physical activity, and vigorous physical activity can be determined [36]. Participants will wear the actigraph for 1 week.

Emotional Distress

The level of emotional distress is examined with the Hospital Anxiety and Depression Scale (HADS) [37], which consists of 14 items. Each item is scored on a 4-point scale, and the total score ranges from 0 to 42, where a higher score denotes more psychological distress. The HADS includes 2 subscales with each 7 items measuring anxiety and depression with scores ranging from 0 to 21. A subscale score of ≥8 is an indicator of depression or anxiety in patients with TBI, which is in line with findings of the general population [60]. The HADS is a reliable measure and has been validated in the TBI population [61].

Cognitive Complaints

The Dysexecutive Questionnaire Revised (DEX-R) is used to assess cognitive complaints [38]. This questionnaire examines cognitive problems in daily life as experienced by the patient. The DEX-R assesses 4 domain-general types of dysexecutive problems (metacognition or social cognition, executive cognition, behavioral-emotional self-regulation, and activation) and comprises 34 items. Each item is scored on a 5-point Likert scale on how often certain difficulties related to cognition are experienced. The total score ranges from 0 to 136, where a higher score denotes more cognitive problems. The DEX-R is a reliable and valid measure [38,62] and has been used in the TBI population [63].

Participation

The Utrecht Scale for Evaluation and Rehabilitation-Participation (USER-P) [39] is used to assess participation. The questionnaire measures 3 aspects of participation: frequency of behaviors, experienced participation restrictions due to health condition, and satisfaction with participation. The USER-P consists of 31 items across the 3 subscales. Each sum score of a scale is converted to scores ranging from 0 to 100, where higher scores indicate good levels of participation (higher frequency, fewer restrictions, higher satisfaction). The USER-P is a valid and reliable measure in patients with brain injury, and test-retest reliability and internal consistency of the USER-P are satisfactory [64].

Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS) is used to assess social support [40]. The MSPSS consists of 12-items examining perceived social support from family, friends, and significant other. Each item is rated on a 7-point Likert scale. The mean total score ranges from 1 to 7, where a higher score denotes more perceived social support. The MSPSS has shown good psychometric properties [40], and it has been used in TBI patients [65].

Secondary Outcome Measures

Previous research has shown a discrepancy between objective and subjective measures of fatigue and sleep in TBI population [21,25]. Therefore, as the secondary aim, objective measures of fatigue and sleep are included in this study.

Fatigue is measured objectively with the 10-min psychomotor vigilance task (PVT), which is a sustained-attention, reaction-time task, often used in sleep and fatigue research [42]. The PVT is a simple, reliable, and sensitive task for measuring performance and attentional deficits due to fatigue [66]. When performing the PVT, the response time to visual stimuli occurring at random interstimulus intervals is measured. The task has good psychometric properties, has been validated, and has been used in TBI patients [67].

Sleep problems are examined objectively with the actigraph described previously that measures sleep-wake patterns during 1 week. Actigraphy has shown to be a satisfactory objective estimate of sleep especially for global sleep parameters including

total sleep time, sleep onset latency, and sleep efficiency [41]. Multiple studies have included actigraphy to examine sleep in TBI patients [25,68,69], and they have shown that actigraphy is a reliable method for monitoring sleep in this population, irrespective of the injury severity [70].

Group Characteristics and Monitoring Participants

Injury-Related Characteristics

Information regarding the injury such as time since injury, injury severity parameters (eg, intracerebral abnormality on structural imaging data, LOC, PTA, injury severity score), causes of injury, comorbid (physical) injuries, seizures, and drug or alcohol intoxication during injury will be retrieved from the hospital database.

Demographics

The demographic questionnaire asks about age, gender, education, marital status, level of occupational achievement, psychological, and medical history. In addition, this questionnaire assesses medication, drugs, and alcohol use.

Daytime Sleepiness

The Epworth Sleepiness Scale (ESS) is used to examine daytime sleepiness [43]. The ESS measures general level of daytime sleepiness and sleep propensity with 8 items. Each item is scored on a 4-point scale indicating the chance of dozing off, and the total score ranges from 0 to 24, where a higher score indicates more daytime sleepiness. A score of ≥11 indicates clinically significant subjective sleepiness [43]. The ESS is widely used in TBI research [71] and has a reasonably high reliability [72].

Multidimensional Aspects of Fatigue

The Dutch Multi-Factor Fatigue Scale (DMFS) is used to measure the multidimensional aspects of fatigue. The DMFS is a newly developed questionnaire that examines several factors of fatigue following TBI, including impact of fatigue, mental fatigue, signs and direct consequences of fatigue, physical fatigue, and coping with fatigue [44]. The DMFS consists of 38 items rated on a 5-point Likert scale, with higher scores on each subscale indicating more severe fatigue. This questionnaire is specifically developed to measure the multiple facets of fatigue following acquired brain injury [44].

Subjective Sleep-Wake Patterns

The relevant questions of the consensus sleep diary, which is a standardized sleep diary developed by insomnia experts [45], are used to examine subjective sleep-wake patterns and for better interpretation of actigraphy data. The sleep diary includes the following core questions: (1) the time of getting into bed; (2) the time at which the individual attempted to fall asleep; (3) sleep-onset latency; (4) duration of awakenings; (5) time of final awakening; (6) final rise time; and (7) perceived sleep quality (rated via Likert scale) [45]. An additional question about napping/dozing is added. The diary is completed in the morning and is filled out for 7 consecutive days concurrent with the actigraphy. Sleep diaries are a reliable and validated measure to examine sleep [73].

Posttraumatic Stress Disorder

The presence of posttraumatic stress disorder (PTSD) is determined with the PTSD Checklist of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; PCL-5), a 20-item self-reported measure corresponding to the DSM-5 symptom criteria for PTSD [46]. Each item is rated on a 5-point scale Likert scale and the total score ranges from 0 to 80, where a higher score denotes more severe PTSD symptoms. A score of 33 or higher is suggested as the indication of PTSD [46]. The PCL-5 is a reliable measure with strong validity [74]. PTSD occurs in 18% to 27% of the cases following severe TBI [75,76]. To check whether PTSD is the underlying cause of elevated stress and as PTSD takes time to develop, the PCL-5 is only assessed at visits 2 and 4.

Coping Style

Passive reaction coping style and active problem-solving coping style are examined with the Utrechtse Coping Lijst (UCL), which will differentiate active approach versus passive approach [47]. As this study only includes active and passive coping, the questionnaire will consist of 14 items scored on a 4-point Likert scale. Scores for both subscales range from 7 to 28, where higher scores denote a higher preference for that coping style. Both subscales show fairly good internal consistency and reasonably high test-retest reliability in the Dutch population [77]. The UCL has been used in Dutch TBI patients before and showed limited variability over time, therefore, coping styles are only assessed at visits 1 and 4 [78].

Sleepiness Preceding the Task

Sleepiness before the PVT is assessed with the Karolinska sleepiness scale (KSS) [48]. The KSS consist of 1 item on a 9-point Likert scale ranging from extremely alert to very sleepy, great effort to keep awake, where a higher score denotes greater sleepiness. The subject indicates the sleepiness level of the preceding 5 min. The test-retest reliability and the construct validity of the KSS are high [79].

Statistical Analyses

Descriptive statistics will be used to present mean scores and SDs at each time point of the outcome measures and predictive variables. Normality and assumptions will be checked. Next, 2 linear mixed regression analysis [80] will be performed to evaluate the associations between the predictive (independent) variables (pain, cognitive impairment, physical activity, emotional distress, cognitive complaints, social support, and participation) and the primary end point (subjective sleep quality and fatigue) across time. For each of the 2 primary end points, we will first determine whether these associations with predictors change across the 4 time points (ie, time by predictor interactions). In case of a significant interaction, simple interaction contrasts comparing consecutive time points will be used to determine whether the association between predictor and primary end point decreases or increases. Bonferroni correction will be used to adjust for multiple testing.

For the secondary objectives, the temporal relation between objective fatigue, objective sleep, and the predictive variables of the biopsychosocial model will be examined with the same

linear mixed-effects regression analyses as used for the primary objectives.

Results

Recruitment of participants for this longitudinal cohort study started in October 2017, and the enrollment of participants is ongoing. The first results are expected at the end of 2020.

Discussion

This study describes the protocol of a longitudinal cohort study examining fatigue and sleep following moderate to severe TBI and the underlying predictors with a biopsychosocial model.

There are several reasons why this cohort study is innovative. First, this study has a longitudinal design. To the authors' knowledge, there are only 3 longitudinal follow-up studies examining fatigue or sleep following moderate to severe TBI in the first 12 to 24 months post-TBI [22,81,82]. These studies had a much smaller sample size and focused on fatigue or sleep separately.

Second, even though fatigue and sleep are closely related, they can be affected independently, and problems with fatigue and sleep do not always co-occur [15]. Therefore, this study examines fatigue and sleep concurrently in a follow-up design to better understand their common and unique manifestations, as was also recommend by Cantor et al [15].

Third, this study uses a biopsychosocial explanation of post-TBI fatigue and sleep problems [9]. Multiple researchers suggested integrated biopsychosocial approaches for future studies to best explain the outcome of TBI [83-86]. However, few studies have yet examined multiple identified biopsychosocial factors in a comprehensive model over time to determine the significant underlying factors that contribute to post-TBI fatigue and sleep problems. Understanding these complex interactions is crucial to establish, explain, and treat fatigue and sleep problems associated with TBI.

Finally, this study uses both subjective and objective measures to examine fatigue and sleep. Previous research has shown discrepancies between objective and subjective measures of fatigue and sleep in the TBI population [21,25]. Therefore, it is important to include both measures. However, most studies only include subjective or objective measures of fatigue and sleep.

A limitation of this study is that the extreme, severe multitrauma patients will not be included in the study because they may not be recognized as TBI due to severe multiple physical injuries and they may not be able to participate due to their injuries. This may jeopardize the generalizability of the results to all moderate to severe TBI patients.

To the authors' knowledge, this study will be the first that examines the development of both post-TBI fatigue and sleep longitudinally with a biopsychosocial model in moderate to severe TBI and that will differentiate between fatigue and sleep using both subjective and objective measures. Identification of modifiable factors such as mood and psychosocial stressors may give direction to the development of interventions for fatigue and sleep problems post-TBI that subsequently lower the burden for the patient and may prevent the development of secondary symptoms and complaints such as depression.

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Authors' Contributions

All authors contributed to the design and the protocol of the study. All authors reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

COWAT: controlled oral word association test
DMFS: Dutch Multi-Factor Fatigue Scale
DEX-R: Dysexecutive Questionnaire Revised
ESS: Epworth Sleepiness Scale
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
KSS: Karolinska sleepiness scale
LOC: loss of consciousness
MSPSS: Multidimensional Scale of Perceived Social Support
PCL-5: PTSD Checklist for DSM-5
PSQI: Pittsburgh Sleep Quality Index
PTA: posttraumatic amnesia
PTSD: posttraumatic stress disorder
PVT: psychomotor vigilance test
SDMT: symbol digit modalities test
TBI: traumatic brain injury
UCL: Utrechtse Coping Lijst
USER-P: The Utrecht Scale for Evaluation of Rehabilitation-Participation (In Dutch: Utrechtse Schaal voor Evaluatie van Participatie)

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Protocol

Health Disparities and Converging Epidemics in Jail Populations: Protocol for a Mixed-Methods Study

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Abstract

Background: Incarcerated populations have increased in the last 20 years and >12 million individuals cycle in and out of jails each year. Previous research has predominately focused on the prison population. However, a substantial gap exists in understanding the health, well-being, and health care utilization patterns in jail populations.

Objective: This pilot study has 5 main objectives: (1) define recidivists of the jail system, individuals characterized by high incarceration rates; (2) describe and compare the demographic and clinical characteristics of incarcerated individuals; (3) identify jail-associated health disparities; (4) estimate associations between incarceration and health; and (5) describe model patterns in health care and jail utilization.

Methods: The project has two processes—a secondary data analysis and primary data collection—which includes a cross-sectional health survey and biological sample collection to investigate infectious disease characteristics of the jail population. This protocol contains pilot elements in four areas: (1) instrument validity and reliability; (2) individual item assessment; (3) proof of concept of content and database accessibility; and (4) pilot test of the "honest broker" system. Secondary data analysis includes the analysis of 6 distinct databases, each covered by a formal memorandum of agreement between Northern Arizona University and the designated institution: (1) the Superior Court of Arizona Public Case Finder database; (2) North Country Health Care; (3) Health Choice Integrated Care; (4) Criminal Justice Information Services; (5) Correctional Electronic Medical Records; and (6) iLEADS. We will perform data integration processes using an automated honest broker design. We will administer a cross-sectional health survey, which includes questions about health status, health history, health care utilization, substance use practices, physical activity, adverse childhood events, and behavioral health, among 200 Coconino County Detention Facility inmates. Concurrent with the survey administration, we will collect Methicillin-resistant and Methicillin-sensitive *Staphylococcus aureus* (samples from the nose) and dental microbiome (*Streptococcus sobrinus* and *Streptococcus mutans* samples from the mouth) from consenting participants.

Results: To date, we have permission to link data across acquired databases. We have initiated data transfer, protection, and initial assessment of the 6 secondary databases. Of 199 inmates consented and enrolled, we have permission from 97.0% (193/199)

to access and link electronic medical and incarceration records to their survey responses, and 95.0% (189/199) of interviewed inmates have given nasal and buccal swabs for analysis of S. aureus and the dental microbiome.

Conclusions: This study is designed to increase the understanding of health needs and health care utilization patterns among jail populations, with a special emphasis on frequently incarcerated individuals. Our findings will help identify intervention points throughout the criminal justice and health care systems to improve health and reduce health disparities among jail inmates.

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KEYWORDS

behavioral health; chronic illness; health status; health care utilization; incarceration; infectious disease; jail; recidivism

Introduction

> *County jail systems, throughout the United States, are more of a broken public health system, and less of an effective justice system than anyone assumes. That condition should be effectively changed on both directions, criminal and public health.* [Criminal Justice Coordinating Council director]

In the last 2 decades, jail and prison populations of the United States have increased markedly in size and diversity [1,2], with a concomitant impact on public health. More than 20 million Americans are currently or have been previously incarcerated, with 12 million cycling in and out of jails each year [3,4]. In addition, there are significant nationwide racial and ethnic disparities in the criminal justice system; 60% of jail and prison populations are ethnic and racial minorities, although they make up just 30% of the general US population [1,3,5]. Prison and jail minority populations are disproportionately burdened by higher rates of substance abuse and poor mental health, as well as chronic and communicable diseases [3,6-8], with considerable rates of comorbidity [8] creating complex prevention and treatment conditions for these institutions. Compared with the general population, prison inmates have a higher burden of mental and neurological disorders, have high levels of stress, anxiety, sleep deprivation, and depression and have lower levels of self-efficacy as a result of the stigma and loss of social ties associated with being incarcerated [7-12]. Rates of many chronic diseases in US jails and prisons are more than double of those in the general population—diabetes (5.0% vs 2.4%), chronic respiratory conditions (eg, chronic obstructive pulmonary disease, 34.1% vs 19.2%), and liver disease (10% vs 0.6%) [3]. Similarly, the rates of communicable diseases, such as hepatitis C, HIV, and tuberculosis [5,13], are higher in incarcerated populations (eg, 3.5% vs 0.4% for HIV among 25-34-year olds) [14]. Women [15], ethnic minorities [16], and older adults [17] are considered particularly at-risk for poor health outcomes in the jail system. Furthermore, people who do not have a permanent residence in between jail stays face greater risk of mortality because of treatable conditions [18].

Previous research on incarceration and health has predominately focused on relatively stable prison populations, in spite of the potentially greater impact of jail incarceration on public health and population health conditions. In contrast to prison populations, jail populations are considerably more transient and more likely to interact regularly with the general population. The average length of jail stays is 8-10 days, with a small percentage of the populations staying for up to 1 year or longer awaiting trial [19,20]. The shorter-term stay and release from jail can be a destabilizing public health force for individuals and communities, making them more likely to relapse to substance abuse and nonadherence to mental and physical health treatment programs [21]. In addition, they become an equally important potential vector for a communicable disease being cycled in and out of jail populations. Continuity of care is severely impacted by cycling between jail and community and is associated with a limited opportunity for stability in health care [22]. By federal regulation, Medicaid benefits, which provide insurance for a disproportionate number of inmates prior to their incarceration, are suspended or even eliminated upon incarceration [22,23]; this creates a barrier to continuity of care for many chronic conditions, treatment regimens for severe mental impairments (SMI), and other behavioral health problems, because of benefits being temporarily or permanently terminated, as well as marked differences in the formularies offered by the jail as opposed to those offered by Medicaid benefits.

Nationwide, high health care utilization among criminal justice system populations has been observed both before and after incarceration. The risk of hospitalization is higher following release from correctional facilities compared with the general population [24]. Over 80% of recently released jail and prison inmates have chronic mental, behavioral, and substance abuse issues, and 85% of these individuals rely on the emergency department to address acute episodes rather than seeking primary care from a physician [25-27]. Similarly, >50% of recently released jail inmates reported using emergency departments as their primary source of health care in the 3 months before jail incarceration, and 75% reported using acute care services at any time before being incarcerated [17]. Furthermore, to the best of our knowledge, no study has assessed the impact of the implementation of the Affordable Care Act and the Affordable Care Act's Medicaid expansion on health care utilization among incarcerated individuals.

Textbox 1. Diseases of interest.

Infectious diseases

- Hepatitis C
- HIV/AIDS
- Gonorrhea
- Syphilis
- Chlamydia
- Tuberculosis
- Methicillin-resistant *Staphylococcus aureus*, Methicillin-sensitive *Staphylococcus aureus*

Cardiovascular diseases

- Ischemic heart disease
- Heart failure
- Acute myocardial infarction
- Stroke or transient ischemic attack
- Atrial fibrillation
- Anemia

Pulmonary diseases

- Chronic obstructive pulmonary disease
- Asthma

Cancer

- Colorectal
- Endometrial
- Breast (female and male)
- Lung
- Prostate
- Leukemia and lymphomas

Other chronic diseases or conditions

- Chronic back pain (lumbago)
- Chronic kidney disease
- Diabetes
- Hypertension
- Hyperlipidemia
- Liver disease, cirrhosis, and other liver conditions (except viral hepatitis)
- Migraine and chronic headache

Mental disorders and behavioral health

- Depression
- Depressive disorders
- Bipolar disorder
- Anxiety disorders
- Alcohol use disorders
- Drug use disorders
- Autism spectrum disorders

- Intellectual disabilities and related conditions
- Learning disabilities
- Schizophrenia
- Posttraumatic stress disorder

Table 1. The demographic information of Coconino County compared with Arizona and the United States, 2016.

Demographic information	Coconino County (N=138,064)	Arizona (N=6,728,577)	United States (N=318,558,162)
Race, n (%)			
Non-Hispanic white	75,521 (54.7)	3,734,360 (55.5)	195,276,153 (61.3)
Black	1,933 (1.4)	3,297,000 (4.9)	42,368,236 (13.3)
Native American or Alaska Native	37,968 (27.5)	363,343 (5.4)	4,141,256 (1.3)
Hispanic	19,053 (13.8)	2,079,130 (30.9)	56,703,353(17.8)
Other	3,590 (2.6)	222,043 (3.3)	20,069,164 (6.3)
Language other than English spoken at home, n (%)	33,550 (24.3)	1,809,987 (26.9)	66,897,214 (21.0)
High school graduate, n (%)	122,049 (88.4)	5,786,576 (86.0)	276,189,926 (86.7)
Median household income, US $	50,234	50,255	53,889
Persons in poverty, n (%)	26,922 (19.5)	1,103,487 (16.4)	40,456,887 (12.7)
Population per square mile	7.2	56.3	87.4
Uninsured (<65 years), n (%)	20,157 (14.6)	8,000,7001 (11.9)	32,174,374 (10.1)

Surveillance of both chronic and acute illness, intervention, and coordination of support services has the potential to improve health within the jail system [28,29], interrupt cycles of recidivism [30], and provide necessary continuity and support for transitions from jail to the community [27]. In addition to surveillance and targeted intervention programs, effective intervention points are needed to disrupt the cycle of homelessness and recidivism and address the comorbid occurrence of substance abuse and mental health issues [21,31,32]. Northern Arizona, specifically Coconino County, is particularly well-suited for studying the confluence and flow between the criminal justice and health care systems.

Unlike large metropolitan areas with multiple different hospital systems and emergency departments, Coconino County is a relatively isolated population with a single major health care system, single incarceration unit, and limited variability in public health resources.

Both secondary data analyses of linked criminal justice and health care system databases in Northern Arizona and the prospective health disparities survey of inmates, described below, are anticipated to provide information on racial and ethnic health disparities associated with a variety of chronic diseases, communicable diseases, and behavioral health issues. We have identified several diseases of interest (Textbox 1) and will determine the local rates of these targeted diseases and associated health disparities in Northern Arizona using the International Classification Diseases, Ninth and Tenth Revision Clinical Modification codes. Locally focused disparity research is essential in gaining an understanding of the population dynamics driving regional health care burdens. The population of Northern Arizona has a unique composition in that the number of American Indians is much higher compared with the United States as a whole (27.5% vs 1.3%), and Arizona ranks 10th in the country for our uninsured population (Table 1) [33]. Higher representation of American Indians will provide sufficient statistical power to examine the needs of this underserved population.

The protocol described in this study is directed at understanding the longitudinal view of health care utilization before, during, and after jail incarceration. Results from assessing the complex trajectories of emergency department, behavioral health services (Regional Behavioral Health Authority), and public health services use (Department of Health) among individuals with high rates of recidivism, inmates characterized by a high number of jail admissions and discharges, will provide for targeted modeling of possible public health interventions for this population.

Evaluating and modeling the impact of individuals with high rates of recidivism on public health, using a “converging epidemics” or Syndemics Theory Approach [34], as opposed to a single condition epistemology, should allow us to identify multiple points for intervention, using a multisectoral rather than unintegrated approach to prevention and intervention. Understanding the comprehensive and interconnected needs, conditions, and health service utilization trajectories of the broken public health system in jails has significant potential to produce new models of intervention, effective policy change, and collective action.

Methods

Overview

The Health Disparities in Jail Populations project began, as demonstrated in the opening quote above, as a community-engaged research project with a strong interdisciplinary focus, including a partnership between Northern Arizona University's (NAU) Center for Health Equity Research, School of Informatics, Computing, and Cyber Systems, College of Social and Behavioral Sciences, and the Coconino County Criminal Justice Coordinating Council (CJCC) [35]. The confluence of existing expertise in chronic disease, communicable disease, and behavioral health, as well as the social determinants of health among underserved populations, provides a unique opportunity for research and positive impact on our ability to intervene in population health issues and model potential areas of prevention and intervention in critically underinvestigated groups.

The operational questions framing the study, identified below, focus on the empirical definition of criminal justice recidivists, the social determinants of existing health disparities in a jail population compared with nonincarcerated individuals, the convergence of high-impact utilization patterns for health services in and out of jail, and identifying intervention points to address public health conditions for the incarcerated population.

We are guided by the Social Determinants of Health framework [36] to identify, assess, and develop our initial and evolving research questions on existing health disparities among jail populations. The Social Determinants of Health framework allows for exploration of the complex intersections of social-, cultural-, economic-, and system-level influences on health and well-being. The research questions framing this feasibility study are as follows:

Research Questions

Our research questions are as follows:

1. Empirically define recidivists: What is the distribution of the number of incarcerations, lengths of stay, and other characteristics of multiple incarcerations for the population cycling through the Coconino County Detention Facility?
2. Describe and compare characteristics of incarcerated individuals: What are the demographics and socioeconomic characteristics of persons in the jail system?
3. Identify jail-associated health disparities: What are the incidence and prevalence rates for targeted diseases and conditions in the jail population and general health care populations in Northern Arizona? Are health disparity issues more similar to prison populations or the general population?
4. Describe associations between incarceration and health: Are incarceration variables (eg, length of stay, type of criminal activity, risk level, ability to post bail, and the number of incarcerations) associated with health outcomes and disease severity in jail populations?
5. Model patterns in health care and jail utilizations and identifying opportunities for intervention: What is the health care and jail utilization over the life span of incarcerated individuals and compared with the general population?
6. The project is functionally separated into two data collection and analysis processes that address the overarching questions above—(1) a comprehensive secondary data analysis component and (2) a primary data collection effort that includes a cross-sectional health survey component that incorporates self-reported information, collection of biological samples, and data from the available secondary databases.

Secondary Data Analysis of the Coconino County Detention Facility Inmates

Our focus for the secondary data analysis will be county-level data derived from the 6 listed data sources. The primary focus for the analysis is the Coconino County Detention Facility in Flagstaff, Arizona. The Coconino County Detention Facility provides inmate housing for local, state, and federal law enforcement agencies and courts in Northern Arizona; it is a regional holding facility that houses both sentenced and unsentenced misdemeanor and felony offenders. The Flagstaff facility has an operating capacity of 477 beds (477/596, 80.0% of the total available beds is considered operating capacity because of inmate security classification requirements). Northern Arizona's demographics differ from those of Arizona's and the US population (Textbox 1); thus, results may not be generalizable to state and national populations but may be generalized to populations with a high proportion of minority residents and populations with high uninsured and poverty rates.

A subset of our analytical population will be individuals with high rates of recidivism in the jail system. We will conduct literature searches for established definitions of jail recidivism in public policy, political science, law, and public health literature, as well as conducting an empirical assessment of criminal justice databases on incarceration. We have created an analytical framework that allows us to determine the impact of multiple incarcerations on the health status of individuals. The incarceration data are available in both the secondary analysis datasets, and the datasets that are linked to the inmate survey. Because characteristics of inmates differ with varying lengths of stay (eg, a difference between inmates incarcerated for 1 day compared with inmates awaiting trial for over a year), when characterizing inmates and modeling inmates' health care utilization, we will stratify our results by meaningful categories based on the length of stay. In addition, we will categorize inmates meaningfully by the length of stay and other incarceration characteristics when estimating associations between incarceration and health and identifying health disparities. To inform our decision on an empirical definition of recidivists, using criminal justice databases, described below, we will describe the characteristics and distributions of arrests, incarcerations, and recidivism among Coconino County Detention Facility inmates. Measures will include frequency of arrests, the frequency of incarcerations, total time incarcerated, and average length of stay in the Coconino County Detention Facility.

The secondary data analysis efforts are centered on descriptive analyses of 6 distinct databases from 5 participating partners:

1. The Superior Court of Arizona public database provides case information (Public Case Finder) for incarceration and court history from 177 of the 184 courts in Arizona and includes all Coconino County courts. The Case Finder database includes birthdate, case number, case title, offense category (traffic, noncriminal ordinance, criminal, etc), court filing date, judge, disposition date (and appearance status), citation description, closed date, and case activity.
2. Criminal Justice Information Services (CJIS) is a database provided by a division of the Federal Bureau of Investigation containing criminal history data. Each state has a repository for criminal history information that feeds into the CJIS division system. The Coconino County Adult Probation Department provided access to the Arizona Computerized Criminal History System, which contains all arrest and court results (eg, convictions and not guilty verdicts) for offenders within Arizona that get reported to the CJIS. The CJIS contains 23,340 individuals aged ≥18 years from January 1, 2010 to December 31, 2014.
3. iLEADS is the Coconino County Detention Facility's inmate record system. The system automates the incarceration process from booking, screening, classification, and release. It is the primary system used by the jail to track information about an inmate. iLEADS contains 79,506 individuals aged ≥18 years from January 1, 2007 to May 31, 2018.
4. Correctional Electronic Medical Records is the Coconino County Detention Facility's electronic medical records system. This database is used by medical staff within the jail to track medical history during incarceration.
5. North Country Health Care Electronic Health Records is the electronic medical record system utilized by the North Country Health Care System. North Country is the Federally Qualified Health Center for Northern Arizona and provides primary and oral health care to 14 communities in Northern Arizona. This database contains records from primary care visits, dental visits, obstetrician-gynecologist and pregnancy visits, laboratory results, and diagnoses that can be associated with incarceration records for Coconino County. North Country Health Care contains 117,301 nonduplicated individuals from January 1, 2010 to December 31, 2014.
6. The Health Choice Integrated Care is a collaboration between Health Choice, the managed care solutions division of IASIS Healthcare, and the Northern Arizona Regional Behavioral Health Authority, a managed care organization that has served the behavioral health needs of Northern Arizona residents for >50 years. Their electronic medical records database contains integrated health care (medical and behavioral) records for members with SMI and provides the primary behavioral and SMI records.

Several procedural steps are required to allow successful secondary data analysis of the databases, including (1) creating and testing a secure transfer and data storage process compliant with the Institutional Review Board (IRB), Health Insurance Portability and Accountability Act of 1996 (HIPAA), Criminal Justice, and other federal privacy and confidentiality regulations for data with personal health information and personal identifying information to the secure project server; (2) conversion of the databases to an appropriate analytical format (SAS, SPSS, etc); (3) exploratory data analysis of each database (ie, acquisition or creation of an appropriate data dictionary, review of the quality of the data, and including missing data); (4) assessment of the database for variables that are relevant to the research questions; (5) identification of all variables that can be used to link the datasets; and (6) data cleaning as necessary.

The databases described above will be integrated to provide a longitudinal view of an individual across multiple community-based health providers, criminal justice databases, and jail-based health services. We will perform data integration for the databases by using an honest broker design [36]. The automated honest broker process has the following three general steps: (1) creating a unique identifier for each individual present in each database; (2) identifying common individuals across databases, and establishment of a single identifier for each individual; and (3) propagating the individual identifier to the source databases, and the removal of all identifying information, save for the unique identifier, from the source databases. We have implemented and pilot-tested a version of the automated honest broker system to determine the feasibility of linking the datasets for the full (interagency and interinstitution) database integration. The honest broker algorithm is designed to look for and match records that represent the same entity or person across disparate databases; this algorithm generates matches by 3 variables—name (first and last), Social Security Number, and date of birth. The algorithm was tested first on linking 2 datasets, containing 40,000 and 250,000 unique individuals or "records," respectively. The algorithm found 10,815 matches between both datasets. A third dataset was added with 105,000 individuals, and the algorithm found 7740 matches among all 3 datasets.

The advantage of this design is threefold: (1) it establishes a persistent key as the identifier, which can then be populated back to source systems to enable further analysis or interventions to be tracked across systems, providers, and time; (2) provides an enhanced level of assurance for privacy and adherence to IRB standards and protocols; and (3) separates analysis process and analysts from bias associated with individually identifiable data, while allowing the incorporation of individual-level covariates, predictors, and outcome variables to be visible.

Cross-Sectional Health Survey Among Coconino County Detention Facility Inmates

We will conduct a cross-sectional health survey among 200 Coconino County Detention Facility inmates housed at the Coconino County Detention Facility. The survey includes questions about (1) basic demographic information of respondents, (2) respondents' experience with the criminal justice system, (3) health care utilization patterns of respondents, (4) epidemiology of communicable disease, chronic illness, and behavioral health issues, and (5) health behaviors (eg, physical activity and smoking). The survey will take participants approximately 1 hour to complete.

Prior to any data collection for the jail project, investigators are required to complete the Prison Rape Elimination Act training and a volunteer safety training. Training included safety procedures and regulations within the Coconino County Detention Facility. In addition, investigators are under an

obligation or a "duty to inform" when an inmate poses a threat to either themselves or others. Finally, to preserve confidentiality, audio monitoring and recording are suspended during survey sessions. However, there are special security considerations that include video monitoring.

Participants will be recruited from the Coconino County Detention Facility based on a stratified purposive, sampling strategy [37]. The detention center consists of 4 pods (F Pod, A Pod, B Pod, and C Pod) with a total of 21 dorms containing 28-32 beds per pod. The dorms are segmented by sex (male and female), by an internal risk assessment evaluation (low, medium, and high security), and by known conflicts among inmates. We will recruit between 12 and 15 individuals per dorm. We established a total recruitment target of 200 individuals (approximately 33.6% (200/596) of the total available beds, and 41.9% (200/477) of the operational census for the facility) to achieve a representative sample of the population.

The inclusion criteria for the survey includes (1) being currently incarcerated in the Coconino County Detention Center in Flagstaff, AZ; (2) being aged ≥18 years; (3) being able to read English; and (4) providing informed consent for participation. The exclusion criteria are (1) being aged <18 years of age; (2) having residence in a restricted dormitory in the jail; and (3) having a decision to not provide informed consent for participation. Individuals will be excluded if they are unable to consent because of cognitive impairment. The 4 restricted dormitories include dorms housing juveniles being charged as adults, an "administrative confinement" dorm, a dorm for individuals diagnosed with SMI that are not considered competent to consent to participation, and an administration dorm that houses protected individuals, such as former officers. There will be no exclusion on the basis of sex, ethnicity, or health status. Our study involves a vulnerable population—county jail inmates. Persons with SMI and homeless individuals will not be specifically targeted but will not be excluded. Owing to the high comorbidity of SMI and substance abuse in jail populations [38], we anticipate enrolling these individuals. Finally, pregnant women may be part of the jail population, and although not specifically targeted, pregnant women will not be excluded. The confidentiality of the vulnerable populations will be maintained just as for our entire population. We will store all research information on secure data servers by encrypting the data and the server as a whole, as well as by limiting access to all data to key research personnel only. No individuals will be identified or identifiable in reports or publications.

Recruitment

A study team member and a jail staff member will describe the project to a dorm's inmates. Interested participants who meet the eligibility requirements will be assigned a time to complete the survey in groups of 5. During a scheduled session, Coconino County Detention Facility personnel will escort inmates to a program room equipped with a one-way mirror, video (but not audio) recording, chairs and tables, and materials used for programs. Before beginning, a study team member will review the consent form with participants. The consent form includes 3 sections as follows: (1) study survey; (2) collection of biological samples (see Collection of Biological Samples among Coconino County Detention Facility Inmates below); and (3) permission to access jail medical records. If an individual does not consent to the study survey, they will be escorted back to their pod. Participants may continue if they do not consent to the collection of biological samples and access to jail medical records. Following consent, individuals will be given a second-generation iPad to complete the survey on the Qualtrics Office Survey Application (Provo, UT), a platform for administering surveys without an internet connection. If, at any given time, an individual no longer wishes to participate, they will be thanked for their participation and escorted back to their dorm, and any partial data will be erased from the iPad. For participants who consented to the biological sample collection, once an individual completes the survey, a team member will retrieve the iPad and begin collecting biological samples. Upon completion, participants will be thanked for their participation and will be provided with US $15 in commissary privileges or a gift card added to their personal belongings and accessed after release from jail. Participants will then be escorted back to their dorm. After completion of data collection, a jail nurse will provide Correctional Electronic Medical Records data to researchers for participants who consented to this aspect of the study.

Instrument Development

The survey instrument is comprised of items and scales adapted from existing national health surveys of general populations [39], other measures of relevant health, and well-being constructs with high previously demonstrated validity and reliability [40], as well as instruments targeted at assessing incarcerated populations [41]. The final instrument includes questions relating to a broad list of health domains; specifically, a range of communicable diseases, commonly occurring chronic conditions, issues related to behavioral health and well-being, and other related constructs (eg, global self-rated health status), as well as a comprehensive set of questions assessing demographic and socioeconomic characteristics. The majority of the questions are taken from (1) the National Health Interview Survey [42], (2) the National Health and Nutrition Examination Survey [39], (3) the Behavioral Risk Factor Surveillance System [43], (4) Behavioral Risk Factor Surveillance System Adverse Childhood Experiences module [44], (5) Patient Health Questionnaire [45], (6) International Physical Activity Questionnaire [46], and (7) the National Inmate Survey [47]. In reviewing the candidate items for the instrument, we found that the majority of the health surveys exclude inmates from their sampling framework; most also do not identify the previous incarceration.

An initial instrument was assessed through a pilot cognitive debriefing process [48,49], to ensure (1) a consistent understanding of questions across participants, and (2) an alignment of participants' understanding of items with the original intent of the questions. The interviews were administered to 4 undergraduate students attending NAU. Survey items that were problematic tended fall into the following 3 categories: (1) uncertainty about definitions of items or recognition of some diseases; (2) the request for additional questions; and (3) the desire for additional response options (eg,

add “internet” as a response option to the question querying the type of place one goes to for health care). To keep the integrity of well-validated questions, we were unable to accommodate items of the third type. However, we were able to accommodate concerns of types 1 and 2 and, subsequently, constructed the final version of the instrument.

The final instrument was piloted with a volunteer group of 5 individuals incarcerated in the Coconino County Detention Center to see whether any significant issues were surrounding the use of the instruments in a jail population. The instrument validity and individual item comprehension were assessed through a small pilot test (5 inmates) and debriefing process. We wanted to determine whether there were any significant problems with reading level, item comprehension, the sensitivity of questions (especially alcohol and drug questions), and the range of time it took to complete the survey (between 25 and 50 minutes for this group). The pilot test indicated that even the slowest reader could complete the survey in the allotted time. Reading comprehension was generally acceptable; participants requested further clarification about 3 of the diseases listed, and the alcohol and drug questions were not considered sensitive. We will conduct a sensitivity analysis for all items and scales in the instrument, as this type of analysis has not been conducted for jail populations.

Collection of Biological Samples Among Coconino County Detention Facility Inmates

The survey administration detailed above will be accompanied by biological sampling from the nose and mouth of volunteer participants. Nasal samples will be assayed for carriage of *Staphylococcus aureus* (both Methicillin-resistant and Methicillin-sensitive *S. aureus*), while oral samples will be evaluated for the presence of the known dental caries-causing bacteria, (*Streptococcus sobrinus* and *Streptococcus mutans* samples from the mouth). Each of these bacterium is known to be elevated nationwide in prison populations [50] and Northern Arizona’s general (nonincarcerated) population. The biological sample collection will allow us to build an important database on the interaction of 2 public health conditions that are of high salience for this population and potentially allow us to differentiate between the general detention population and recidivists.

To collect *S. aureus* samples from the nose, a participant will use a sterile, single-tipped swab flocked with soft nylon fiber (Fisher Scientific, catalog # 22-349-700) to gently rub the inside of both nostrils with the swab head for 1-2 seconds. The samples will be processed at NAU’s Pathogen and Microbiome Institute by a trained wet-lab technician. The technician will use standard aseptic techniques to inoculate (streak) a HardyCHROM *S. aureus* plate (Hardy Diagnostics, p/n G311). The swab will be stored, and should the original streaking process fail to yield bacterial colonies, the swabs will be used to restreak another plate. Our previous efforts (unpublished pilot data) indicate that ~30% of Northern Arizona residents are positive for *S. aureus*. As a result, we anticipate that ~30% of the samples (60 of 200) will be positive for the bacterium. We alternatively expect, based on increases in prison populations, that significantly >30% of samples will be positive.

To collect *S. sobrinus* and *S. mutans* samples from the mouth, a participant will use a sterile, single-tipped cotton swab to gently rub the swab along the gum line of the upper and lower jaw, spending approximately 1-2 seconds on each tooth. Similar to above, a trained wet-lab technician will use standard aseptic techniques to streak a partitioned HardyCHROM plate containing media for *S. sobrinus* on one side and *S. mutans* on the other side (Hardy Diagnostics). Based on the previous work, up to 40% of Northern Arizona residents have one or more decayed teeth, with an unknown fraction of those being carriers for *S. mutans* and *S. sobrinus* (data not published). As a result, we anticipate that up to 40% of our samples (80 of 200) will be positive for, at least, one of the caries-causing bacteria, specifically, preliminary data indicates 10-20 positives for *S. sobriunus*.

Results

To date, we have established the feasibility in the acquisition of highly restricted databases, including permission to link data across those databases across multisectoral institutions that have not been previously linked. We have successfully completed memoranda of agreements for each database, allowing for “public health research” on the databases. We have accomplished the data acquisition, transfer, conversion, and variable assessment on the 6 secondary databases and are scheduled to complete that process for all databases within 60 days. In addition, we have demonstrated the feasibility of gaining access to the jail population and have IRB approval for both the secondary data analysis (NAU IRB approval: 934185) and the prospective data collection (NAU IRB approval: 1067490), as well as linking both prospective and secondary data sources for our survey population using the automated honest broker system.

Discussion

The combined protocols for the 2 complementary approaches present a number of procedural and methodological challenges that are not often present in common jail or public health services frameworks. A primary challenge includes identifying appropriate existing databases that both singly and collectively allow us to address the following 5 interconnected research questions: (1) empirically defining the jail population segments in ways that allow us to compare and contrast the general population with recidivists; (2) describing and comparing characteristics of Coconino County Detention Facility inmates; (3) identifying incarceration-associated health disparities for communicable disease, chronic illness, mental health, and substance abuse in jail populations; (4) describing critical associations between incarceration information (such as number of incarcerations) and health and disease; and (5) linking individuals across these datasets, through the use of an honest broker system, in a way that allows us to understand the health services impact of recidivists. Although many databases were explored, databases not included were found not applicable to our study questions or not accessible.

The second primary challenge was acquiring ethically appropriate access and federally sanctioned protection for the

databases. All databases are "owned" by public or semipublic institutions and require a "community-based" approach for data acquisition. In addition, each database contains personal identifying information and personal health information of inmates, a federally recognized vulnerable population. Federally recognized vulnerable populations require additional data safety protocols beyond the Common Rule and HIPAA compliance. Several databases were removed from consideration because of refusal by the owner. However, our assessment of the included databases suggests the existing data configuration is appropriate to achieve the overall goals and objectives of the project. Each database required the creation of a separate memorandum of understanding and a complex data-sharing protocol. Each memorandum of understanding includes a set of common data acquisition and data protection procedures that are (1) project-based, and (2) IRB- and HIPAA-approved.

Developing the health survey in the jail presented additional challenges, including the design and development of a valid data collection instrument. Candidate questions were drawn from a variety of nationally deployed surveys (see above for full listing). We discovered very few of the psychometrically validated health-related instruments have been adapted to prison or jail populations. As an example of the need for adaptation, questions on physical activity (International Physical Activity Questionnaire) include explanatory examples such as shoveling snow, riding a bicycle, taking a walk, etc; those examples do not effectively exemplify activities available in a jail exercise area. Similarly, questions regarding social interactions may be problematic because of limited opportunities to interact with family and friends outside of jail. Time-restricted questions pose similar problems. The average length of incarceration is 8-10 days [19,20]. Thus, if we are interested in, for example, the impact of incarceration with depressive symptoms measured by questions such as, "Over the past two weeks, have you been bothered by any of the following problems?," Patient Health Questionaire-9 [45], we may not be able to distinguish the level of depression prior to incarceration from the level of depression during incarceration, as the 2-week period may include both conditions for inmates. To determine the appropriateness of our instrument, we will apply basic psychometric analyses and post hoc sensitivity analyses to examine the validity and reliability among jail inmates. This work will allow us to determine whether future studies should develop new instruments designed specifically for jail inmates or can appropriately modify existing questions adapted to jail incarceration.

One of our working assumptions is that jails may not be an appropriate venue to conduct prevention and intervention programs in all 4 areas of the converging epidemics in our study (chronic illness, behavioral health, communicable disease, and substance abuse) and that some multisectoral approaches are needed to address public health needs of this population comprehensively. At the same time, jails may play a pivotal role in addressing the overall impact of incarceration on public health. We believe a multisectoral or collective impact framework will be necessary to reduce the "broken public health" system in jails. As a consequence of these intersecting conditions, we aim to produce a model for prevention and intervention programs in all 4 areas of health, potentially resulting in a marked cost reduction for health care among inmates.

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Conflicts of Interest

None declared.

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Abbreviations

CJCC: Criminal Justice Coordinating Council

CJIS: Criminal Justice Information Services
HIPAA: Health Insurance Portability and Accountability Act of 1996
IRB: Institutional Review Board
NAU: Northern Arizona University
SMI: severe mental impairment

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Protocol

Hearing Aid Use in Older Adults With Postlingual Sensorineural Hearing Loss: Protocol for a Prospective Cohort Study

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Abstract

Background: Older adults with postlingual sensorineural hearing loss (SNHL) exhibit a poor prognosis that not only includes impaired auditory function but also rapid cognitive decline, especially speech-related cognition, in addition to psychosocial dysfunction and an increased risk of dementia. Consistent with this prognosis, individuals with SNHL exhibit global atrophic brain alteration as well as altered neural function and regional brain organization within the cortical substrates that underlie auditory and speech processing. Recent evidence suggests that the use of hearing aids might ameliorate this prognosis.

Objective: The objective was to study the effects of a hearing aid use intervention on neurocognitive and psychosocial functioning in individuals with SNHL aged ≥55 years.

Methods: All aspects of this study will be conducted at Swinburne University of Technology (Hawthorn, Victoria, Australia). We will recruit 2 groups (n=30 per group) of individuals with mild to moderate SNHL from both the community and audiology health clinics (Alison Hennessy Audiology, Chelsea Hearing Pty Ltd). These groups will include individuals who have worn a hearing aid for, at least, 12 months or never worn a hearing aid. All participants would be asked to complete, at 2 time points (t) including baseline (t=0) and follow-up (t=6 months), tests of hearing and psychosocial and cognitive function and attend a magnetic resonance imaging (MRI) session. The MRI session will include both structural and functional MRI (sMRI and fMRI) scans, the latter involving the performance of a novel speech processing task.

Results: This research is funded by the Barbara Dicker Brain Sciences Foundation Grants, the Australian Research Council, Alison Hennessy Audiology, and Chelsea Hearing Pty Ltd under the Industry Transformation Training Centre Scheme (ARC Project #IC140100023). We obtained the ethics approval on November 18, 2017 (Swinburne University Human Research Ethics Committee protocol number SHR Project 2017/266). The recruitment began in December 2017 and will be completed by December 2020.

Conclusions: This is the first study to assess the effect hearing aid use has on neural, cognitive, and psychosocial factors in individuals with SNHL who have never used hearing aids. Furthermore, this study is expected to clarify the relationships among altered brain structure and function, psychosocial factors, and cognition in response to the hearing aid use.

Trial Registration: Australian New Zealand Clinical Trials Registry: ACTRN12617001616369; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617001616369 (Accessed by WebCite at http://www.webcitation.org/70yatZ9ze)

International Registered Report Identifier (IRRID): RR1-10.2196/9916

(JMIR Res Protoc 2018;7(10):e174) doi:10.2196/resprot.9916

KEYWORDS

sensorineural hearing loss; hearing aids; cognition; psychosocial function; speech processing; fMRI

Introduction

Background

Aging is associated with the onset of postlingual sensorineural hearing loss (SNHL), which refers to hearing loss (or deafness) arising from the pathology of either the inner ear organs or the vestibulocochlear nerve after language acquisition. SNHL accounts for approximately 90% of hearing loss cases in adults and is insidious, progressing from normal (pure tone average [PTA]=0-25 dB) to mild (PTA=26-40 dB), to moderate (PTA=41-70dB), to severe (PTA=71-90 dB), and ending with profound (PTA >91 dB) or total hearing loss. However, more alarming are the sequelae of SNHL that might include rapid cognitive decline [1], impaired psychosocial functioning [2], increased risk of falling [3], and increased risk of incident dementia [4,5]. Recent work, including a meta-analysis of 33 studies [6], reported that SNHL is independently related to both cognitive impairment [7] and the risk of incident dementia [4] and perhaps, most critically, the degree of hearing loss predicts both the degree of cognitive impairment [1] and risk of dementia [4]. Furthermore, recent work suggests that 9% of dementia risk over the life course could be eliminated by avoiding the effects of hearing loss [5].

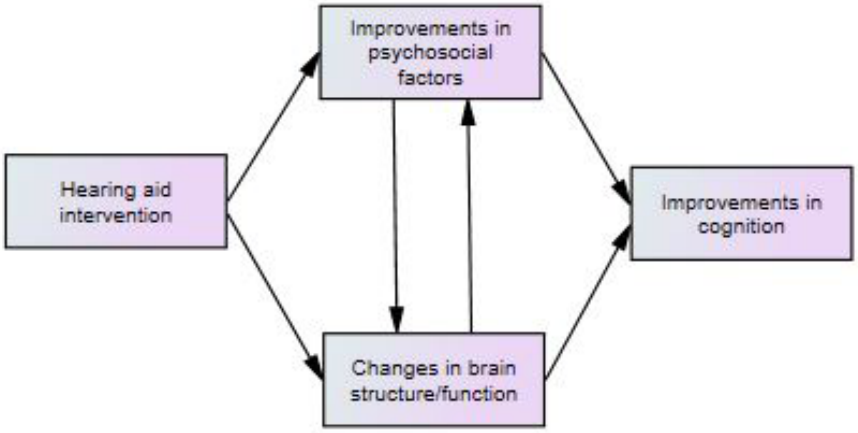
The scale of these problems is brought into sharp focus in the light of SNHL being the most prevalent chronic condition affecting older adults in developed countries (16%-20%) [8-10] and the second leading cause of years lost to disability globally [11]. Sadly, SNHL often goes undiagnosed and untreated or undertreated [12,13], and the sequelae of SNHL, incident dementia in particular, impose a significant burden not only on individuals and their families and friends but also on national health budgets [14,15]. A recent nationwide study in Australia found that all forms of hearing loss affected 14.5% of Australians (3.6 million people), especially those aged >50 years, with direct costs to the Australian economy of almost Aus $15.9 billion [16]. Furthermore, the number of Australians affected is expected to grow to 18.9% of the population by 2060, thereby slowing or stopping the progression of SNHL is a public health imperative.

The mechanisms underlying the links among cognitive decline, dementia risk, and SNHL are unknown but have been proposed to be due to either common neurodegenerative causes [17,18] or downstream neural changes precipitated by the diminished auditory input [1,19]. Core to these hypotheses is the theory that the diminished auditory input profoundly affects speech processing capabilities and consequently, impairs social functioning [12]. Consistent with these sequelae, individuals with SNHL exhibit accelerated brain atrophy compared with normal hearing adults, especially within right temporal lobe structures [20] that are critical for many cognitive functions. These findings are corroborated by reports that patients with SNHL exhibit atrophic and plastic alteration within cortical brain areas that underpin normal speech processing [21,22].

The initial stages of speech processing in normal hearing adults involve the analysis of basic speech sounds, including phoneme (speech sounds made by the mouth, eg, spoon has 4 phonemes; s/p/oo/n) and acoustic processing [23], which occur within the mid and posterior parts of bilateral dorsal temporal lobe structures, including the superior temporal gyrus, superior temporal sulcus, and planum temporale (for excellent review, see [24]). In their model of speech processing, Hickok et al suggested that subsequent higher-level processing, which includes motor (reproduction and planning) and memory (semantic and linguistic) processes and mapping of the initial sensory and phonological output onto the distinct dorsal and ventral neural pathways [24]. In addition, a left-lateralized dorsal articulatory motor network that includes the inferior frontal, premotor, anterior insula, and temporoparietal cortices maps the output onto articulatory representations; moreover, a bilateral ventral pathway that includes the anterior and posterior portions of the middle and inferior temporal lobes (sulci and gyri) map the output onto ventral lexical and semantic representations to facilitate understanding. Of key interest here are the alterations of brain structures that underlie speech processing in patients with SNHL.

Typically, individuals with SNHL adapt to their altered aural predisposition by relying increasingly on visual cues, including lip-reading. In normal hearing older adults, lip and word reading broadly activate the dorsal articulatory and spectrotemporal and phonological analysis networks mentioned above, except the primary auditory cortices due to the diminished auditory function [25]. Furthermore, SNHL adults engage in a similar network but exhibit higher amplitudes in the attendant structures, especially the prefrontal and premotor cortices, and recruit additional structures, including the right posterior temporal lobe [21,26-28], which is normally only activated by actual sounds [25].

Figure 1. Hypothesized relationships associated with first-time hearing aid usage.



This functional alteration is thought to stem from the loosening of associations between memory and phonological processes and viseme (visual aspects of phoneme pronunciation) processes as SNHL progresses [29] (ie, altered functional connectivity), leading to these plastic brain changes. The phonological processing specialization of the left posterior temporal lobe appears to be preserved, whereas right lateral homologues that are predominantly involved in processing environmental sounds are repurposed to accommodate enhanced visual processing that aids the reading of visual cues (eg, lip-reading) and phonological processing capabilities [21,28,30]. Furthermore, the right anterior part of the superior temporal gyrus that normally performs voice and speaker identification functions is also repurposed for reading visual cues; however, this plastic alteration can be reversed by auditory rehabilitation [31].

Fortunately, a recent investigation suggests that hearing aids worn by individuals with SNHL can preserve or improve auditory and cognitive functioning [32-34] in addition to improving psychosocial well-being [33,35-38]. This suggests that stimulation, as afforded by hearing aid use, can preserve auditory functions and aural specificity and that hearing aids have a protective effect against the deleterious plastic alteration of auditory areas [39].

Alarmingly, however, approximately 90% of people with mild hearing loss, approximately 60% with moderate to severe hearing loss, and approximately 70% aged 65-84 years do not use hearing aids [40]. Furthermore, it often takes about 10 years for an individual to recognize that they have a hearing problem and then act, including obtaining hearing aids, to address this problem [41]. Critically, almost two-thirds of older adults with a hearing impairment do not use hearing aids [42].

This prospective cohort study, in which magnetic resonance imaging (MRI) is utilized in combination with clinical, neuropsychological, and hearing tests, aims to investigate the neurocognitive and psychosocial effects of wearing hearing aids in older adults with SNHL (ACTRN12617001616369).

Study Objective

Through this study, we seek to understand whether the use of hearing aids can alter the neurocognitive function and affect beneficial plastic brain changes in individuals with SNHL. In particular, we aim to determine whether early intervention can normalize the function of the speech processing brain network. To this end, we will use neuropsychological, clinical, and psychophysical tests in combination with functional and structural MRI (fMRI and sMRI). In addition, fMRI acquisitions will include scanning during the performance of a speech processing task (detailed later) to probe the function of the speech processing network, besides the resting state fMRI to probe the brain network function more generally, whereas sMRI would enable the assessment of both the volume and integrity of the gray and white matter.

Study Hypotheses

In comparison to the long-term hearing aid users, after wearing a hearing aid for 6 months, the group who have never worn a hearing aid will exhibit improved cognition, reduced depression, improved social interaction, altered activation of the auditory cortices and attendant networks, and altered connectivity between auditory and attendant networks.

In addition, the study will explore any baseline relationships among the cognition, psychosocial, and neural function in participants with and without a hearing aid and any relationships among the improved cognition, psychosocial function, and neural function in participants without a hearing aid after the hearing aid intervention, as seen in Figure 1.

Methods

Study Design

The study is a prospective cohort design evaluating the effect of the hearing aid use on cognition, psychosocial factors (eg, depression and social interaction), and neural function. We will recruit 2 participant groups of similar size consisting of people with mild to moderate SNHL. Of note, group randomization is not possible in this study; however, the groups will be matched as much as possible in terms of the degree of hearing loss.

1. Group A: Patients with SNHL who have used hearing aids for, at least, the previous 12 months and plan to continue using their hearing aids for the next 6 months.
2. Group B: Patients with SNHL who have never used hearing aids before and who will be willing to wear hearing aids for the next 6 months.

All participants would be asked to complete, at 2 time points (t) including baseline (t=0) and follow-up (t=6 months), tests of hearing and psychosocial and cognitive function and attend an MRI session.

Eligibility Criteria

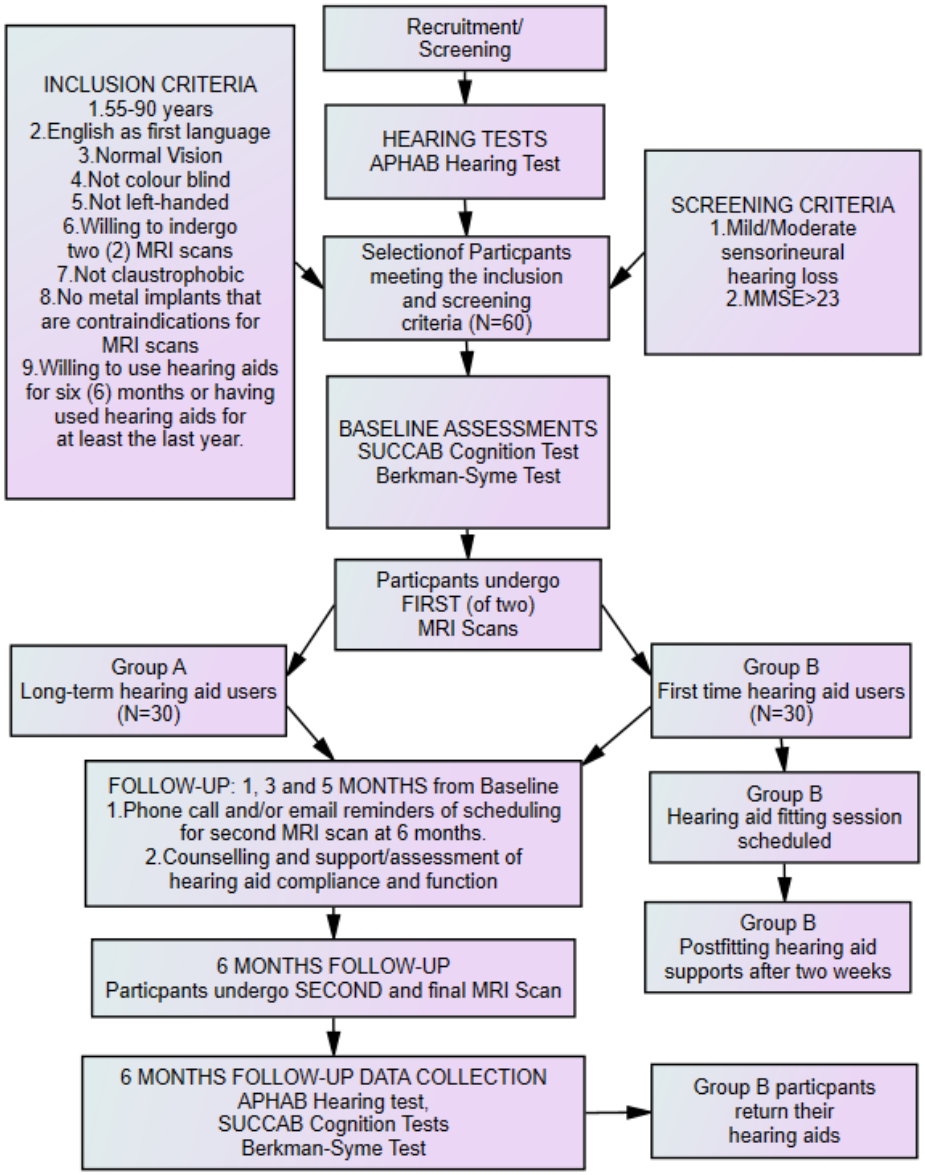
Participants must be aged 55-90 years, speak English as first language, exhibit mild or moderate SNHL with a PTA of thresholds at 0.5-4 kHz in both ears, willing to undergo two 1-hour MRI scanning sessions over a period of 6 months, and willing to wear hearing aids for 6 months or must have been wearing hearing aids for at least 1 year. Furthermore, participants must give written informed consent.

Participants will be excluded if they exhibit left handedness, marked visual impairment that would prevent reading, cognitive impairment (defined as a score ≤23 on the Mini-Mental State Examination, MMSE), severe or profound hearing loss, and MRI contraindications. Figure 2 presents the flowchart of the overall data collection plan.

Recruitment and Screening

Audiology health clinics with existing relationships with the Swinburne University, such as Alison Hennessy Audiology and Chelsea Hearing Pty Ltd, will be contacted to distribute the study promotional material to their clients who have previously undergone hearing assessments at the audiology clinic, been diagnosed with mild or moderate SNHL, and have been wearing their hearing aids for at least 1 year. In addition, the clinic will distribute promotional materials to clients who have recently been recommended to acquire hearing aids but have not yet decided to purchase the aids. All clients who express interest in the study through the audiology clinic will be invited to attend an information session at the Swinburne University of Technology.

Figure 2. Data collection plan for experimental trial. APHAB: Abbreviated Profile of Hearing Aid Benefit; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; SUCCAB: Swinburne University Computerized Assessment Battery.



Participants who live within the Swinburne community will also be contacted by telephone and email by the researchers to explain the study; participants who express interest will be invited to attend the information session at Swinburne University. At the information session, the researchers will explain the purpose and significance of the study. At the same time, participants will complete a screening questionnaire to identify participants who will be willing to undergo hearing assessments, undergo two 1-hour MRI scans, and fulfill the inclusion criteria. Before completing the screening questionnaire, participants must provide verbal consent. Then, selected participants will be provided with a participant information and consent package for review, which will include further detailed information on the study procedure and a consent form. Participants willing to participate in the study will be scheduled for hearing assessment at the audiology clinics. At the hearing appointments, participants will submit their written consent before their hearing assessments, and those who meet the inclusion criteria will be scheduled to undergo their first MRI scan at a mutually convenient time at the Swinburne University of Technology.

Study Power Analysis

With 30 consented participants in each group with a significance level of 5%, the power of 80%, and controlling for age, gender, and level of education, the baseline analysis of covariance (ANCOVA) model for spatial working memory performance can detect effect sizes of d=0.63 for between-group differences. Allowing 10% attrition in the 6-month follow-up period, a sample size of 27 in each group with a significance level of 5% and power of 80%, a significant group-by-time interaction effect can be detected for a large effect size of d=0.77. This study is based on the assumption that an effect size of d

Intervention

Fitting of Hearing Aids in Group B Participants

Group B participants will be fitted with two demonstration hearing aids, known as Unitron Tempus Moxi Fit Receiver-in-the-ear hearing aids (Unitron, Kallang, Singapore). The hearing aids will be fitted by professional audiologists at the participating audiology clinics according to the best practice fitting guidelines including real ear (probe tube) measures to verify the amplification and match the appropriate prescribed amplification (typically using the NAL-NL2 prescription developed by the National Acoustics Laboratory [43]) with further adjustment and fine-tuning based on the users' subjective preferences. In addition, the study audiologists will provide a pamphlet guide on the hearing aid use as take-home materials as well as a verbal explanation on how to use these hearing aids. Furthermore, postfitting support will be provided after 2 weeks to make sure that each participant is progressing with their hearing aids.

Follow-Up Periods After the Baseline Data Collection

During the 6-month waiting period between MRI scans, phone call and email reminders for the second testing session will be sent to all participants at 1, 3, and 5 months. At the same time, counseling and other compliance-improving policies [44-46] will be provided to ensure that participants are wearing their hearing aids. In addition, follow-up checks will be conducted by the audiology clinics every 6 weeks for first-time hearing aid users, during which hearing aid usage data will be downloaded and hearing aids will be restarted. An automatic internet-based data logging function installed in the hearing aids will be used to collect hearing aid usage data, which will be used to monitor and assess hours of hearing aid use by these participants. Furthermore, all participants will be encouraged to set their own goals for the hearing aid use and will be asked to assess how well these goals have been met on a regular basis.

After the 6-Month Follow-Up Period

All participants will return to the audiology clinics for further hearing assessments. Group B participants who received loaned hearing aids will return them. In addition, hearing aid supplier information will be provided to them if they are ready to purchase hearing aids. After hearing assessments, participants will return to the Swinburne University to complete the 6-month follow-up assessments.

Contingency Plan

Participants who decide to withdraw because of some discomfort experienced with hearing aids or do not undergo a second MRI testing will be retained in the study for baseline MRI analyses only. In addition, intention-to-treat (ITT) analyses will be used for other analyses not involving MRI data.

Additional Costs and Reimbursements

No costs would be associated with participating in this research project other than transport costs. All participants will be reimbursed Aus $60 to cover these costs after the completion of the 6-month testing protocol.

Outcomes

Assessments for Study

The assessments selected in this study are categorized as follows: hearing assessments, demographic questionnaire, hearing aid benefit questionnaire, cognitive performance, mood and social interaction assessments, and MRI scanning. All participants enrolled in this study will complete these assessments at the baseline and again after 6 months.

Hearing Assessments

Otoscopy and Tympanometry

Following otoscopy, all participants will undergo tympanometry and acoustic reflex testing to assess the status of the middle ear [47,48].

Pure Tone Audiometry in Each Ear

To understand the degree of hearing impairment, and classify participants according to the type of hearing loss, hearing ability will be measured at threshold frequencies of 0.25, 0.5, 1, 1.5, 2, 3, 6, and 8 kHz (air conduction) and 0.5, 1, 2, and 4 kHz (bone conduction) in both ears. The choice of frequency to be tested corresponds to the amplification range of most modern hearing aids and is consistent with the capturing sensitivity at frequencies affected by SNHL and noise-induced damage. Only participants with either mild or moderate SNHL will be included in this study [47,48].

Demographics

Data on a variety of demographic variables will be collected to describe the characteristics of study participants.

The Abbreviated Profile of Hearing Aid Benefit Inventory

The Abbreviated Profile of Hearing Aid Benefit (APHAB) inventory [49], which is a 10-minute self-assessment inventory, will be used to assess the hearing aid benefit (for normative data, see [50]). The 4 scales of the APHAB will be assessed, namely ease of communication (EC) in favorable environments, ease of communication with background noise (BN), ease of communication with acoustic reverberation (RV), such as listening to sounds in a large room, and aversiveness (AV), which measures negative reactions to environmental sounds such as traffic and alarm bells

The APHAB inventory subscales exhibit acceptable reliability with Cronbach alpha value of .87 (EC), .83 (RV), .82 (BN), and .86 (AV) in unaided conditions, and test-retest correlation coefficients of .80, .65, .71, and .89, respectively [49].

Cognitive Assessments

The MMSE Questionnaire

MMSE will be used to assess cognition and will be administered to test the cognitive functioning. MMSE is a valid and reliable way of globally assessing a limited range of cognitive functions [51]. This examination will test the following 5 areas of the cognitive function: orientation, registration, attention and calculation, recall, and language. Participants who exhibit a confusion state while completing the MMSE questionnaire will be advised that they cannot be included in the trial and will be advised to see their general practitioner.

The Swinburne University Computerized Assessment Battery

The Swinburne University Computerized Assessment Battery (SUCCAB) will be used to assess the cognitive performance. This cognitive test battery will allow the assessment of changes in the cognitive performance of all participants over a period of 6 months. The battery will test contextual memory, immediate recognition, simple reaction time, choice reaction time, congruent stroop, incongruent stroop, spatial working memory, and delayed recognition memory. The reliability and validity testing of this battery has demonstrated that SUCCAB is sensitive to aging and has been shown to be particularly effective for measuring short-term changes in cognition of the elderly [52]. Furthermore, SUCCAB correlates strongly with memory subsets in the Wechsler Adult Intelligence Scales [53].

Psychosocial Assessments

Depression, Anxiety, and Stress Scale

Depression, Anxiety, and Stress Scale (DASS) is a well-established self-rating mood scale for measuring 3 related negative emotional states of depression, anxiety, and stress. To assess changes in mood in this study, DASS-21, which is a shortened version (21 items) of the full DASS (42 items), will be used [54]. DASS-21 exhibits excellent subscale reliability with Cronbach alpha of .94 for depression, .87 for anxiety, and .91 for stress [55] and has been validated against other well-established measures, including the Beck Depression Inventory, the Beck Anxiety Inventory, and the State-Trait Anxiety Inventory [55].

The Berkman-Syme Social Network Index

The Berkman-Syme Social Network Index (SNI) [56] will be used to assess participants' social interaction and connections with families and friends. In this study, 12 types of social relationships will be assessed, namely relationships with a spouse, parents, parents-in-law, children, other close family members, close neighbors, friends, workmates, schoolmates, fellow volunteers, members of groups without religious affiliation, and religious groups. Although SNI is commonly used in epidemiological research [57], no detailed assessments exist of its reliability, even if the originators reported an overall value of .92 in a 14-week follow-up study of 245 first-year university students [56]. Because SNI relies on self-report, its validity relies on the honesty of participants.

Magnetic Resonance Imaging Assessments

Speech Processing Task

During fMRI scanning, participants will view a series of human faces (1 male and 1 female actor) that mouth words in blocks (or "epochs") lasting 16 seconds (1 word per 2 seconds) each. Each block will be one of 4 conditions termed *matched* (MAT), *mismatched* (MIS), *no sound* (NOS), and *control* (CON), preceded and followed by 10-second rest periods, where a fixation cross ("+") will be displayed. In each of 2 scanning runs, 4 repetitions of each block type (16 total blocks per run) will be presented in a pseudorandom order, each utilizing different word stimuli. The stimulus presentation time for each of the two scanning runs will be 426 seconds (7 minutes 6 seconds); an additional 20 seconds of imaging data will be acquired following the end of the stimulus presentation to allow the hemodynamic response to return to the baseline.

During MAT, the faces will mouth single syllable, high-frequency words (visual stimuli), such as "cat" or "house," and the corresponding audio input (auditory stimuli) will be played through the headphones. During MIS, the stimuli will remain the same, but the mouthed words and auditory stimuli will be semantically unrelated (eg, "cat" is mouthed but "house" is heard). During NOS, the visual stimuli will be presented but not the auditory stimuli. During CON, the faces will be presented but will not mouth the words; instead, they will simply open and close the mouth without auditory stimuli. All participants will be asked to press a button whenever a face appears to ensure participant attendance to the task.

Magnetic Resonance Imaging Scan Acquisition

The MRI scanning session will include the acquisition of 4 different types of scan data while participants lie supine in the scanner wearing MRI-compatible OptoActive headphones (OptoAcoustics). Participants will have either normal or corrected to normal vision using MRI-compatible goggles. These acquisitions will include 2 fMRI scanning runs while participants perform the speech processing task, a high-resolution T1-weighted structural image (~8 minutes), diffusion-weighted images (~10 minutes), and a resting state fMRI scanning acquisition (~10 minutes); the total scanning time will be 42 minutes.

The following details the different scan protocols, including scan parameters, preprocessing, and data analysis:

1. Scan acquisition for the speech processing task will utilize a T2* sensitive echo-planar imaging sequence (repetition time [TR]=2000 ms; echo time [TE]=30 ms; flip angle=90°; field-of-view=192 mm, 46 interleaved slices, 3-mm^3 isotropic voxels). Preprocessing and statistical analysis will be performed using SPM12 and associated toolboxes. Preprocessing will include slice-timing correction, motion correction, coregistration of realigned functional images to structural (T1-weighted) scans, warping ("normalization") of structural and functional scans into standardized stereotactic space, and spatial smoothing of functional images. The data will be modeled by constructing separate regressors that depict the onset and duration of MAT, MIS, NOS, and CON blocks, convolved with the canonical hemodynamic response function supplied with SPM12. Covariates of no interest (eg, image realignment and other noise parameters) will model noise components.
2. Resting state scanning will utilize T2*-weighted images, which will be acquired continuously using an interleaved multiband sequence (multiband acceleration factor=6; bandwidth=1860 Hz/Px; TR=870 ms; TE=30 ms; echo spacing=0.69 ms; flip angle=55°; field-of-view=192 mm; voxel resolution=2 mm x 2 mm x 2 mm; slice-thickness=2 mm; number of slices=66). In addition, multiband acquisition sequences will be derived from the Human Connectome Project [58]. Data analysis will be performed using the "CONN" connectivity toolbox [59] to test changes in the functional connectivity between brain areas we find to be critical in the sensory integration task as a function of wearing the hearing aids, in addition to broader network connectivity. Next, images will be realigned, normalized to a standard stereotactic space defined by the Montreal Neurological Institute (MNI space), spatially smoothed with a 5-mm kernel, and temporally band-pass filtered (0.010-0.100 Hz). T1-weighted images will be segmented into gray and white matter, as well as the cerebrospinal fluid. Then, physiological noise and motion parameters will be regressed from the functional images using ACompCor [60]. Temporal confounds regressed from the time series will include head motion parameters and their temporal derivatives, in addition to ACompCor-derived noise components.
3. The T1-weighted image will be acquired using a magnetization-prepared gradient echo sequence (TR=1900 ms; TE=2.52 ms; flip angle=9°; field-of-view=256 mm x 256 mm; 176 slices; 1-mm^3 voxels). Diffusion-weighted images will be acquired using an isotropic diffusion tensor imaging sequence for fractional anisotropy (FA) estimations (number of directions=60; *b*-value=3000 s/m^2; slice-thickness=2.5 mm; TR=8400 ms; TE=117 ms; flip angle=90°). In addition, T1-weighted images will be used in the coregistration of functional data and also perform the analysis of regional brain volumes using voxel-based morphometry (VBM) using DARTEL procedures. For VBM, images will be manually reoriented and segmented [61], then a template will be created from the reoriented images using the nonlinear deformations that best align the segmented images, which will subsequently be warped into stereotactic space and spatially smoothed.
4. Finally, we will perform diffusion-weighted magnetic resonance (MR) white matter tractography using "MRTrix" [62] to assess white matter tract changes as a function of wearing the hearing aids. Preprocessing steps will include constructing a brain mask, estimating diffusion tensor components, and performing constrained spherical deconvolution. Subsequently, we will perform whole-brain and seed-based fiber tracking.

Auditory Stimuli Input Considerations

As the speech processing task will involve hearing word stimuli, the auditory input for each participant will be tailored to fit a normalized audiogram, that is, the gain will be enhanced at impaired frequencies. This will be performed by fitting a spline function to prerecorded audiograms that will be used to modulate auditory stimuli for the left and right ears separately. Additionally, the headphone output will be modified such that it is consistent across individuals.

Primary Statistical Analyses

In this study, repeated measures mixed model group (no hearing aid vs hearing aid users) x Time (Time 1 vs Time 2) analysis (RMMM) will be used for all analyses. The missing data will be accommodated in this analysis; however, in the case of whole-brain fMRI analyses, only completed protocol participants will be included. In the ITT RMMM analyses, the autoregressive (AR) dependence will be assumed.

Cognitive Data

The SUCCAB performance measure for spatial working memory will be used as the primary SUCCAB measure; this measure has been found to be particularly effective in measuring short-term changes in cognition of the elderly [52] and is calculated by dividing the response accuracy by the reaction time for a spatial working memory task. Using this and other SUCCAB performance measures, baseline values for the 2 groups will be compared using an ANCOVA analysis, controlling for age, gender, and education level. In addition, changes in these values over time will be compared for the 2 groups of respondents using an ITT RMMM, controlling for age, gender, and education level and any variable that differs markedly between the groups at the baseline.

Mood and Social Interaction Data

In this study, the mood will be assessed using the DASS scale, and social interaction will be measured using the Berkman-Syme SNI. The baseline measures for the 2 groups will be compared using analysis of variance. In addition, changes in these measures over time will be compared for the 2 groups of respondents using an ITT RMMM, controlling for age, gender, and education level and any variable that differs markedly between the groups at the baseline.

Neuroimaging Data

Inferences from functional and structural neuroimaging analyses will be assessed using the random field theory to correct for multiple comparisons at the cluster level.

Speech Processing Task Data: Functional Alteration

First, we will compute the contrast of MAT>NOS (NOS controls for viseme processing) for each participant and enter the contrasts into an RMMM to assess the effect of the first-time hearing aid use on speech sound processing; (2) we will assess changes in the functional connectivity in key areas determined from this analysis using the generalized psychophysiological analytic approach [63]; (3) finally, we will use key areas of difference as seeds in the functional connectivity analysis of the resting state data.

Secondly, we will compute the contrast of NOS>CON (CON controls for basic face motion processing) for each participant and enter the contrasts into an RMMM to assess the effect of the hearing aid use on viseme processing; (2) we will assess changes in the functional connectivity in key areas determined from this analysis using the generalized psychophysiological analytic approach [63]; (3) finally, we will use key areas of difference as seeds in the functional connectivity analysis of the resting state data.

Structural T1 Data: Structural Alteration

To assess plastic alteration in response to the first-time hearing aid use, these spatially smooth gray matter images will be entered into an RMMM.

Exploratory Analyses

Cognitive Data

Correlations between the SUCCAB performance measures and neuroimaging data will be investigated at the baseline and after 6 months for each o group using ANCOVA analyses and ITT Hierarchical Linear Model analyses.

Psychosocial Data

Correlations between DASS and the Berkman-Syme SNI with the SUCCAB performance measures and the neuroimaging data will be investigated at the baseline and after 6 months for each group using ANCOVA analyses and ITT Hierarchical Linear Model analyses. In addition, structural equation modeling will be used to explore the role of the mood and social interaction data as process variables for the effects of hearing aid use on the cognition and neural function, testing the hypothesized model shown in Figure 1.

Neuroimaging Data

We will explore changes in phoneme and viseme processing separately and their integration, as a function of the hearing aid use by modeling combinations of MAT, MIS, NOS, and CON, in addition to any change in the functional connectivity using the generalized psychophysiological analytic approach [63]. In addition, we will explore the altered whole-brain connectivity and internetwork coupling using the resting state data. Finally, we will assess the white matter alteration using the VBM approach described above for the gray matter. Furthermore, we will plan to explore changes in the white matter integrity using diffusion tensor analyses and diffusion tractography.

Results

The speech processing task was programmed and tested during September 2017-December 2017. Training of research staff on research protocols (cognitive, hearing, and MRI session testing) was conducted intermittently between February 2016 and February 2020. In addition, the baseline testing sessions will commence in February 2018 and will be completed by June 2020, and the follow-up sessions will be completed by December 2020. Furthermore, baseline session data analyses will be completed by October 2019, and final longitudinal data analyses will be completed by July 2020.

Discussion

Summary

SNHL is strongly associated with cognitive decline, social and mental health problems, and incident dementia. SNHL leads to brain atrophy and neuroplasticity that may be detrimental to auditory rehabilitation. Some evidence indicates that the use of hearing aids may slow or improve this pathology. In this retrospective cohort study, we utilize cognition and psychosocial testing in combination with structural and functional neuroimaging to assess the impact of the hearing aid use on the neurocognitive function and brain structure in those with SNHL. To the best of our knowledge, this is the first study to directly assess structural and functional brain changes arising from the use of hearing aids in older adults with SNHL. Currently, there is a paucity of neuroimaging studies in the SNHL field generally, which is surprising given what is known about neural plasticity in SNHL. A chief motivation for this work is to address this shortcoming, yielding critical data for SNHL research and ideally, may prompt greater use of hearing aids in those with SNHL.

Limitations

This study has some limitations that must be addressed. There are numerous aspects of speech processing, in general, and its impairment in SNHL. In this study, we have chosen to examine the processing of one aspect alone, namely monosyllabic word processing. This approach was selected to make the task easy to perform for participants and to ease data interpretation. Hence, our analyses will not reveal all aspects of speech processing dysfunction in SNHL such as sentence comprehension [64]. In addition, studies examining the cognitive impairment in SNHL have not utilized consistent neuropsychological testing protocols; hence, the component processes probed across studies might not be consistent, inhibiting the generalization of findings across studies. However, here we use a standardized battery that has been found to be particularly sensitive in older adults [52].

Conclusions

SNHL is a major and growing health problem for older adults that touches most aspects of their lives, especially their cognitive function, mental health, and well-being. The use of hearing aids enhances the lives of these individuals through not only enhanced hearing but also improved social interaction, mood, and cognitive functioning. Such day-to-day functional

enhancement in individuals with SNHL suggests that beneficial plastic changes occur in their brains as a consequence of hearing aid use; however, the use of hearing aids among this population is low.

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Authors' Contributions

MEH, JN, HIB, SLR, SB, AP, AH, and DM contributed to the study design and manuscript preparation. DS played a critical role in the technical aspects of the project.

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
APHAB: Abbreviated Profile of Hearing Aid Benefit
AV: aversiveness

BN: background noise
CON: control
DASS: Depression, Anxiety and Stress Scale
EC: ease of communication
FA: fractional anisotropy
fMRI: functional magnetic resonance imaging
HA: hearing aid group
ITT: intention-to-treat
MAT: matched
MIS: mismatched
MMSE: Mini-Mental State Examination
MNI: Montreal Neurological Institute
MR: magnetic resonance
MRI: magnetic resonance imaging
NOS: no sound
PTA: pure tone average
RMMM: repeated measures mixed model
RV: reverberation
sMRI: structural magnetic resonance imaging
SNHL: sensorineural hearing loss
SNI: Social Network Index
SUCCAB: Swinburne University Computerized Assessment Battery
TE: echo time
TR: repetition time
VBM: voxel-based morphometry

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