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Protocol

“Future Patient” Telerehabilitation for Patients With Heart Failure: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cardiovascular disease is the leading cause of mortality worldwide, accounting for 13%-15% of all deaths. Cardiac rehabilitation has poor compliance and adherence. Telerehabilitation has been introduced to increase patients’ participation, access, and adherence with the help of digital technologies. The target group is patients with heart failure. A telerehabilitation program called “Future Patient” has been developed and consists of three phases: (1) titration of medicine (0-3 months), (2) implementation of the telerehabilitation protocols (3 months), and (3) follow-up with rehabilitation in everyday life (6 months). Patients in the Future Patient program measure their blood pressure, pulse, weight, number of steps taken, sleep, and respiration and answer questions online regarding their well-being. All data are transmitted and accessed in the HeartPortal by patients and health care professionals.

Objective: The aim of this paper is to describe the research design, outcome measures, and data collection techniques in the clinical test of the Future Patient Telerehabilitation Program for patients with heart failure.

Methods: A randomized controlled study will be performed. The intervention group will follow the Future Patient Telerehabilitation program, and the control group will follow the traditional cardiac rehabilitation program. The primary outcome is quality of life measured by the Kansas City Cardiomyopathy Questionnaire. Secondary outcomes are development of clinical data; illness perception; motivation; anxiety and depression; health and electronic health literacy; qualitative exploration of patients’, spouses’, and health care professionals’ experiences of participating in the telerehabilitation program; and a health economy evaluation of the program. Outcomes were assessed using questionnaires and through the data generated by digital technologies.

Results: Data collection began in December 2016 and will be completed in October 2019. The study results will be published in peer-reviewed journals and presented at international conferences. Results from the Future Patient Telerehabilitation program are expected to be published by the spring of 2020.

Conclusions: The expected outcomes are increased quality of life, increased motivation and illness perception, reduced anxiety and depressions, improved electronic health literacy, and health economics benefits. We expect the study to have a clinical impact for future telerehabilitation of patients with heart failure.

Trial Registration: ClinicalTrials.gov NCT03388918; https://clinicaltrials.gov/ct2/show/NCT03388918

International Registered Report Identifier (IRRID): DERR1-10.2196/14517

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KEYWORDS

heart failure; telerehabilitation; research design; quality of life; patient education; user-driven innovation

Introduction

Cardiovascular disease is the leading cause of mortality [1-4], accounting for 13%-15% of all deaths worldwide and 24.8% of all deaths in Europe [3]. A majority of cardiovascular disease mortalities are caused by heart failure. Despite advances in heart failure treatment in the past decade, increased lifespan along with obesity and unhealthy lifestyle has caused a continuing increase in the prevalence of heart failure [4,5]. An increase in the prevalence combined with an increasing elderly population has increased the health care costs and the number of people with disabilities [6]. The rehabilitation of cardiac patients aims to improve patients' recovery, functional capacity, psychosocial well-being, and quality of life by using interventions such as physical activity, improved diet, weight control, psychosocial coping, and disease management [3,7,8]. These kinds of lifestyle-based interventions are crucial for patient recovery. However, cardiac rehabilitation programs have poor compliance and adherence [3]. Patients may take their medication regularly, but they find it difficult to alter lifestyle routines. To address this problem, telerehabilitation has been introduced to increase patient participation, access, and adherence with the help of information and communication technology [3,9].

To date, telehealth and telerehabilitation in heart failure has focused on systems that use hemodynamic measurements (ie, blood pressure and pulse), respiration, weight, and subjective questions to assess the risks of worsening heart failure. The responses are sent to health care providers, who then act on these data. Generally, patients do not see their own data. Instead, they wait for a health care provider to communicate to them on whether their heart failure has worsened [10]. A review from 2014 concluded that telemonitoring of patients with heart failure helped minimize decompensation of heart failure in small, single-center use when providers and patients were dedicated or when communication was direct through structured telephone support. However, when telemonitoring was used for the care of populations (in large trials), it proved no better than conventional care [11]. When researchers used questionnaires and qualitative research designs to assess tailored telemonitoring in patients with heart failure, patients reported improved self-care abilities and self-efficacy [12-14].

Patients' preferences and their choice of smart technology in telemonitoring have been assessed in a transatlantic multisite study [15]. Patients with heart failure (n=208) stated that they preferred mobile devices and self-tracking devices for monitoring everyday activity. The use of activity trackers in patients with heart failure had a motivational effect, helping patients increase the number of steps per day [3,16]. In some cases, monitoring daily activity can also be used as predictors of patient health. The Future Patient study [17] described here proposes a new approach in self-management of patients with heart failure by using self-tracking technologies for monitoring physical activity, sleep, respiration, and pulse at night by using low-cost, commercially available, Conformité Européene–marked trackers that can passively "observe" patients in everyday life and make data available for both patients and health care professionals. Based on participatory design [18-20], the Future Patient Telerehabilitation (FPT) program has been developed in collaboration with patients with heart failure; relatives; health care professionals from hospital and health care centers; companies; and an interdisciplinary research team comprising professionals from engineering, psychology, medicine, nursing, and organizational sociology.

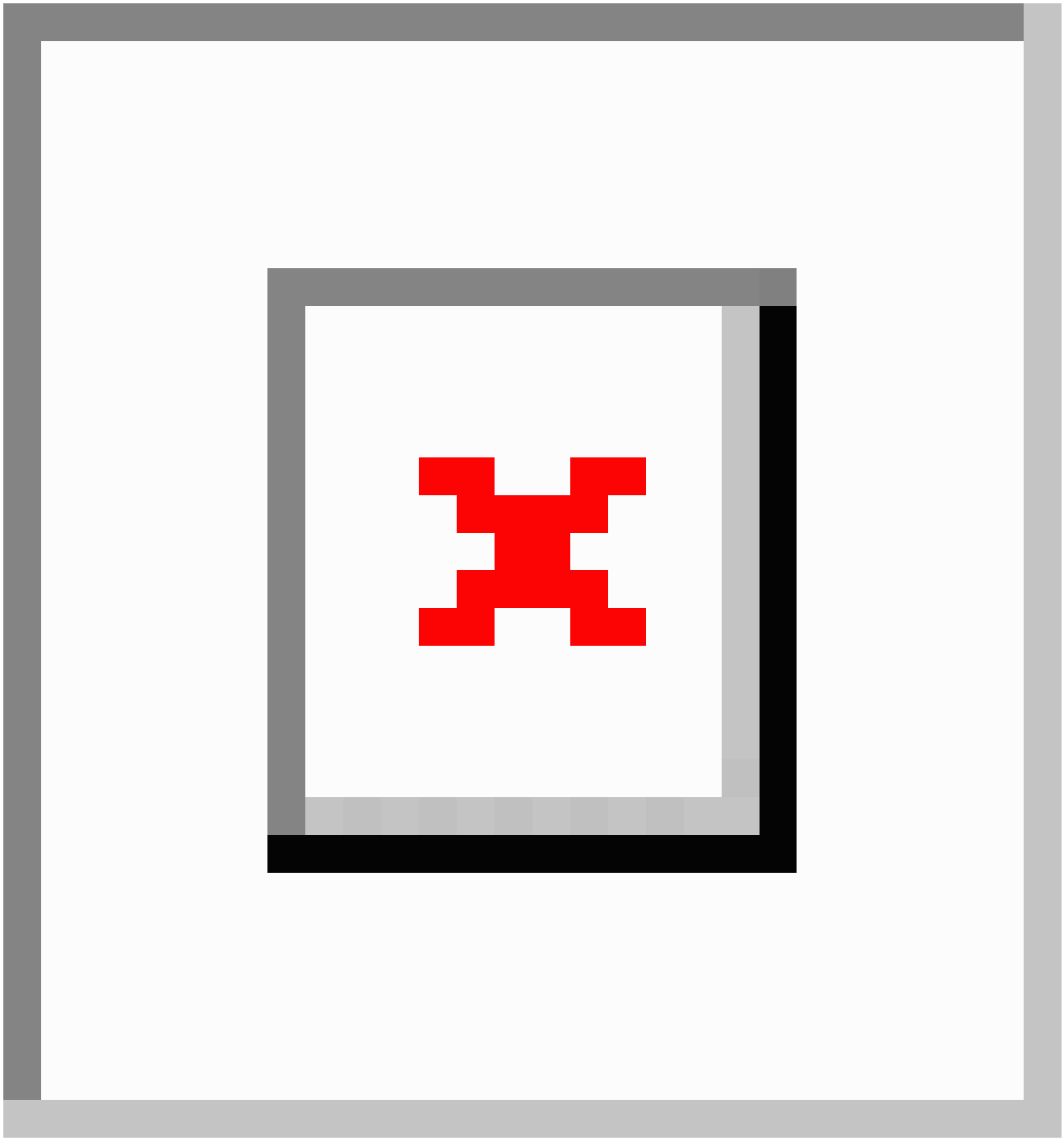
The overall purpose of the FPT study is to develop a telerehabilitation program that helps increase the quality of life of patients with heart failure and educate them to perform individualized monitoring in order to detect worsening of their own symptoms, thereby avoiding rehospitalization. The FPT will be implemented and evaluated in a clinical trial. The aim of this paper is to describe the research design, outcome measures, and data collection techniques used in the Future Patient research project.

Methods

Future Patient Telerehabilitation Program

The FPT consist of three phases: (1) titration of medicine (0-3 months), (2) participation in the FPT at a health care center or call center (3 months), and (3) follow-up with rehabilitation in everyday life (6 months). The three phases of the telerehabilitation program are illustrated in Figure 1.

Figure 1. Telerehabilitation program in three steps.



The HeartPortal

The HeartPortal is a digital toolbox that functions as an interactive learning module; the setup is illustrated in Figure 2, and screen captures are shown in Figure 3. The portal has been developed using a participatory design approach [19,21,22]. The HeartPortal consists of four elements:

Figure 3. Screen captures from the HeartPortal. (A) Front page for the patients. (B) Measurement from the pedometer. (C) The information platform. (D) An illustration of the patient-reported outcome.

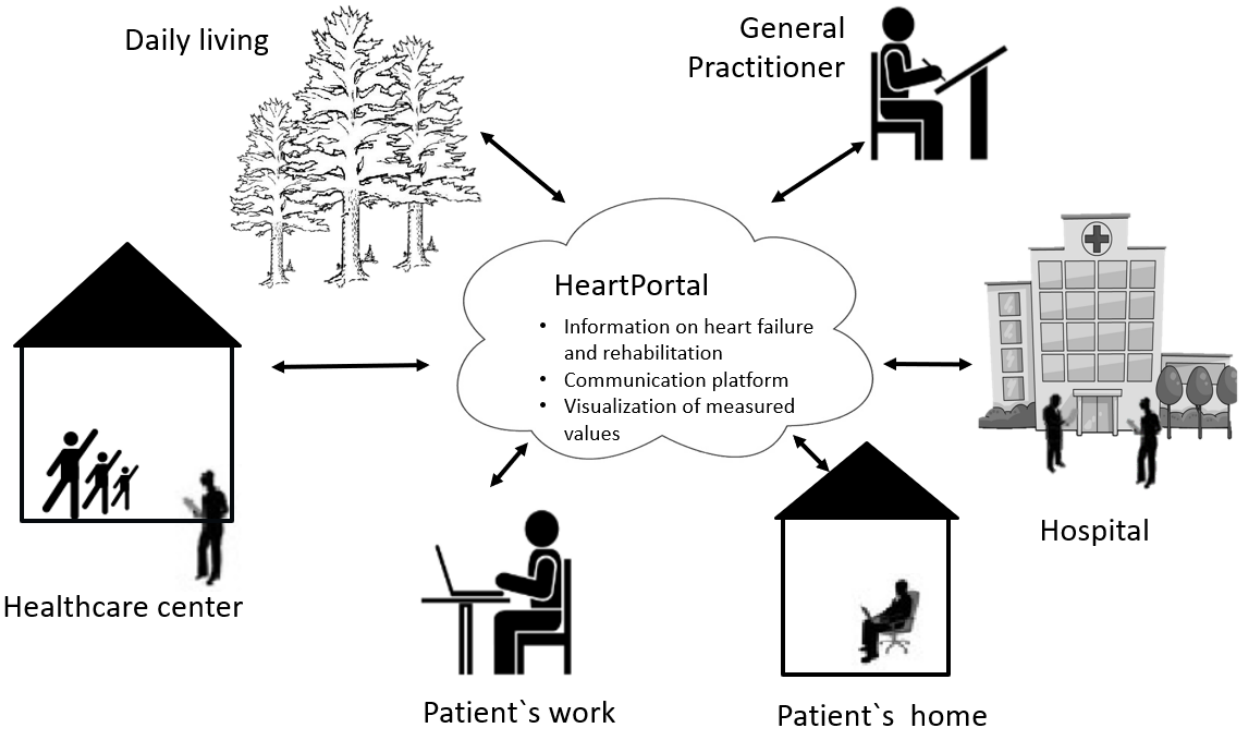
- An interactive information site for patient education, containing information on rehabilitation issues, presented in the form of text and short videos (1-1.5 minutes) with patients and relatives describing their experiences with heart failure, symptoms, living an everyday life with heart failure, etc.
- A communication platform enabling patients to communicate directly with health care professionals. The HeartPortal may be used by health care professionals and patients to collaborate on setting goals and activities, and the patients also have the opportunity to keep an online diary and define their own goals for rehabilitation.
- Visualization of measured values (blood pressure, day and night pulse, weight, respiration, steps, and hours slept).
- Patient-reported outcomes (PRO) data [23]. Every second week, patients complete an online questionnaire about their sleep patterns (Spiegel Sleep Questionnaire) [24]; well-being (three questions defined by the research group); and measures on physical limitations, symptoms, self-efficacy, social interaction, and quality of life using the validated Kansas City Cardiomyopathy Questionnaire (KCCQ) [25,26]. The aim of the PRO-data is to give patients and health care professionals a digital tool to evaluate the patient's current status. The data are presented in the tracking module, thus enabling both patients and health care professionals to view the PRO in all phases of the FPT.

As part of the telerehabilitation program, there is continuous monitoring of the patient's vital signs using technology-enabled devices/equipment. A list of the equipment used is provided below:

- Blood pressure (UA 767PBT; A&D Medical, San Jose, CA) is measured every day during phase I.
- Weight scale (UC-321PBT; A&D Medical, Thebarton, South Australia, Australia) is used only in phase I of the FPT; in phases II and III, patients use their own weight scale. Patients with heart failure measure their weight every day during all three phases of the FPT.
- Data transmitter (QWH-HUB-V1.0E; Qualcomm Life, San Diego, CA) to help transfer data such as blood pressure, day pulse, and weight in a secure form from the devices and to the HeartPortal.
- Step counters (Fitbit Zip or Charge, San Francisco, CA). Patients with heart failure can decide what kind of stepcounter they want to use. Steps are measured every day and transmitted to the HeartPortal.
- Sleep sensor (Beddit 3, Espoo, Finland) measures the numbers of hours of sleep, night pulse, and respiration.
- A tablet (iPad Air 2, Cupertino, CA).

Figure 2 shows how data are presented in the HeartPortal. All the measured values are stored on a secure database at Aalborg University.

Figure 2. The context of the Future Patient study with the HeartPortal at the center.



The patients receive instructions on evaluating their own values and how to react if these values are abnormal. A telerehabilitation coordinator observes all the measured values as well, and during phase 1, the coordinator also acts as a coach, helping patients learn to observe and act on any abnormal readings or worsening of symptoms to avoid possible hospitalization. During phase II, health care professionals also view the data. All health care professionals from the hospital and health care centers have access to the data.

Data and Network Security

There is a strong focus on data and network security in the Future Patient project due to the project's complexity and the environment where data are generated from both the health system (pulled data) and the patients (pushed data). Based on different endpoints in the setup (patient's home, workplace, health care center, etc), the technology used, and the classification of information, the formation of metadata will be addressed via reliable integration encryption and infrastructure reliability.

Eligibility Criteria

The target group in this study consists of patients diagnosed with heart failure according to the New York Heart Association (NYHA) class I-IV [27]. Patients with heart failure are recruited from the Cardiology Wards at hospitals in Skive, Viborg, Silkeborg, and Randers, all situated in the central region of Jutland, Denmark. The inclusion criteria are that the patient must have had a heart failure–related hospitalization within the past 2 weeks; have a stable internet connection at home; and have the ability to sign an informed consent form. Patients may have a pacemaker, and a maximum of 20% of the target group may belong to NYHA class I. Exclusion criteria are a revascularization or open-heart surgery within 3 months prior to inclusion; presence of previous neurologic, musculoskeletal, or cognitive disability or active psychiatric history (as noted in the medical record) other than depression or anxiety related to cardiac or other chronic illness; and absence of basic Danish language skills. All data from the recruitment process and patient withdrawal or dropout will be documented in a consort diagram.

Research Design

The FPT will be tested in a multicenter randomized controlled trial (RCT) using a mixed method [28] approach. The intervention group will participate in the FPT, while the control group will follow a traditional rehabilitation program at the health care center, which is structured according to the national cardiac rehabilitation guidelines [29]. Enrollment of patients began in December 2016, and the RCT will end in September 2019.

Power Calculation

The sample size was defined based on a power calculation. The aim of this project is to increase the quality of life (QoL) using telerehabilitation compared to usual rehabilitation. Based on the official KCCQ guidelines [25], the power calculation estimated the number of participants needed to show an increase in QoL on a scale of 0-100. When using the KCCQ, a "moderate" improvement is equal to a 10-point increase. The target group in the study includes patients with heart failure of a severe degree. As such, a 10-point improvement in the KCCQ will denote a change in the quality of life for the individual patient. Assuming normal distributions and a power of 80%, the number of participants in each group should be 63. However, accounting for 10% dropout, the total number of patients needed for this study is 140. Hence, we plan to enroll 70 patients with heart failure in the intervention group and 70 patients with heart failure in the control group.

Theoretical Framework

The FTP program was designed using the self-determination theory (SDT) as a theoretical starting point. With the goal of increasing the effectiveness of behavior change interventions [30], SDT offers a framework for understanding the role of individualization in motivation. In particular, SDT highlights how fulfillment of basic needs such as autonomy, competency, and relatedness are necessary for initiating and maintaining changes in lifestyle and health behavior over time [31]. If motivation is sustained only by external factors, the patient will not have sufficient incentive to self-regulate and independently maintain a healthy lifestyle. However, if the patient finds that their health behavior goals are in accordance with their own internal values and beliefs (autonomy), the patient will feel that he/she possesses sufficient knowledge and skills to achieve this health behavior successfully (competency) and will feel supported by others (relatedness). The patient will, in turn, experience intrinsic motivation, that is, motivation based on internal factors enabling the patient to maintain the required lifestyle and health behavior over time [31].

Ethics

The Future Patient project has been approved by the Regional Ethics Committee (N-20160055) and the Danish Data Protection Agency. The study is listed in listed in ClinicalTrials.gov (NCT03388918). The study is being carried out in accordance with the Helsinki Declaration, and all participants have signed an informed consent form prior to enrollment in the study.

Baseline Data

Baseline data on demographics, clinical status, primary and secondary diagnosis, NYHA class, and actual prescribed medicines are being collected for both the intervention and control groups (Table 1). Questions on smoking, alcohol consumption, physical activity, IT competences, and rehabilitation will be asked in both groups in the RCT as well.

Outcome Measures

Primary and secondary outcome measures as well as the dates when they the data will be collected are shown in Table 1. The data collection process is described below.

Quality of Life

QoL is the primary outcome, which is measured using the KCCQ [25]. KCCQ is a 23-item self-administered questionnaire and includes different clinical domains such as physical limitations, symptoms, self-efficacy, social interaction, and quality of life. The score is calculated by assigning an ordinal value to each response, beginning with 1, and then adding up to make up a scaled score for each domain. Missing responses are assigned a value corresponding to an average of the answered items within the domain. Scale scores are transformed into a 0-100 range. In the intervention group, the QoL is measured at baseline and then every second week throughout the duration of the program. In the control group, QoL is measured at baseline, 6 months, and 12 months.

Progression in Clinical data

All measured clinical data including weight, blood pressure, pulse (day/night), steps, sleep, and respiration in the intervention group will be collected and analyzed.

Illness Perception

Changes in illness perceptions are being evaluated for both groups using the Brief Illness Perception Questionnaire (Brief IPQ) [32]. The Brief IPQ is a nine-item scale questionnaire designed to rapidly assess the cognitive and emotional representations of illness. Five of the items assess cognitive illness representation, two items assess emotional representation, and one item assesses illness comprehension. The last item is a causal question that asks the patient to list the three most causal factors in their illness. All items except one, the causal question, are scored on a scale from 0 to 10. The measure of the Brief IPQ is compared between groups at baseline, 6 months, and 12 months.

Type of Motivation

Changes in the type of motivation are measured using the Health Climate Change Questionnaire (HCCQ) [33]. The HCCQ is a 15-item questionnaire that assesses patients' perceptions of the degree to which their health care providers are supportive of their autonomy. Respondents rate each statement on a seven-point Likert scale (from "Not at all true" to "Very true"). The total score is calculated by averaging the values of each item. The HCCQ can be used in its full version (15-items) or short version (6-items). In this study, the full version is used. The scores from HCCQ are compared between groups at baseline, 6 months, and 12 months.

Anxiety and Depression

Symptoms of anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire [34]. HADS is a 14-item self-reported questionnaire consisting of two 7-item subscales measuring anxiety and depressive symptoms (ie, it does not assess somatic symptoms). Each item is scored on a four-point Likert Scale from 0 to 3. Scores are tabulated for each subscale, resulting in a score of 0-21, with higher scores indicating higher levels of anxiety or depressive symptoms. The measures from HADS are compared between groups at baseline, 6 months, and 12 months.

Health and eHealth Literacy

Patients' health and electronic health (eHealth) literacy skills are measured using a Danish validated version of the eHealth literacy assessment toolkit (eHLA) [35] and the eHealth Literacy Questionnaire (eHLQ) [36]. The eHLA is a toolkit used to assess health literacy and digital literacy. The toolkits consist of seven tools, four health related and three digitally related, that are either self-reported, such as questionnaires, or a performance test of relevant skills [35]. The eHLQ is a 35-item 7-scale questionnaire used to evaluate and understand how patients interact with digital health services [36]. The measurement of health and eHealth literacy skills is compared between groups at baseline, 6 months, and 12 months.

Table 1. Primary and secondary outcomes.

Outcome and measurement	Time of measurement					Group	
	Baseline	6 months	12 months	End of study	Continuous	Intervention	Control
Primary							
Quality of life	✓	✓	✓			✓	✓
Secondary							
Development of clinical data in intervention group			✓		✓	✓	
Illness perception	✓	✓				✓	✓
Type of motivation	✓	✓	✓			✓	✓
Anxiety and depression	✓	✓	✓			✓	✓
Health and eHealth[a] literacy	✓	✓	✓			✓	✓
Patients' experiences		✓	✓			✓	
Economic evaluation				✓		✓	✓

[a]eHealth: electronic health.

Use of and Experiences Using the HeartPortal

Qualitative exploration of patients', their relatives', and health care professionals' experiences using the HeartPortal will be conducted. Semistructured interviews inspired by Brinkman and Kvale [37] will be conducted after 6 months and 12 months. To analyze which parts of the HeartPortal are being used and for how long, time log files for login/logout of patients and relatives will be analyzed. The patients and relatives will be asked for their consent to extract their log files from the database for analysis.

Economic Evaluations

A cost-effectiveness analysis will be based on the guidelines for economic evaluation by Drummond et al [38]. Estimates of the mean costs per patient will be made with a broad societal perspective, including use of resources for patients, hospital, and municipality. Estimation of costs will be based on data at the patient level for all patients, both at the intervention and control groups.

Data Analysis

All demographic data are being stored in the Future Patient database (FPD). Data from questionnaires are stored in Research Electronic Data Capture software [computer software] (Nashville, TN: Vanderbilt University) and used for quantitative analysis.

Adverse Events and Dropout

All adverse events, including deaths, dropouts, or withdrawals from the study will be recorded and documented. If the patients no longer want to participate in the study, they can withdraw their consent at any time, and the reason for withdrawal will be documented. In this case, the project team will collect the equipment upon request. Patients who do not participate actively in the intervention will still be included in the study and analyzed according to the intention-to-treat approach. These patients will be allowed to retain use of the project equipment for as long as they want. Technical problems with the equipment will be recorded and documented.

Statistical Analysis

At baseline, descriptive statistics [39] will be reported as median with 25th-75th percentiles in the case of skewed distribution or mean (SD) for normally distributed continuous variables. The nonparametric Kolmogorov-Smirnov test will be used to investigate normality of the distribution. An intention-to-treat analysis on all the randomized subjects will be conducted to provide unbiased comparisons between the intervention and control groups in order to avoid the effects of dropout.

The analysis of change in QoL, anxiety and depression, self-determination, illness perception, type of motivation, and health and eHealth literacy tests will be performed using data acquired through questionnaires. Comparison of incidence rates will be used to investigate the differences between the intervention and control groups. Two-sided tests and a significance level of 0.05 will be used.

All events from the day after randomization to patient exit will be included, while any other evident outcomes will be measured as changes from baseline to all assessment time points. Changes in the other evident outcomes will be tested using linear mixed models. Linear mixed models allow repeated measures to be collected in a longitudinal design and are superior when dealing with dropouts compared to other methods used for repeated measures. Hence, it will not be necessary to use imputation techniques on missing data. Statistical analyses will be performed using SPSS [computer software] (version 25.0. Armonk, NJ: IBM Corp), and values of $P<.05$ will be considered significant for all tests.

Qualitative Analysis

All interviews will be transcribed into text files by a research assistant. The data will be coded in NVivo [computer software] (version 12.0. Melbourne, Victoria, Australia: QSR International; 2018), with inspiration from the SDT theoretical framework and based on methods developed by Brinkman and

Kvale [37]. Two researchers will conduct the interviews and analysis of the data. The date will be presented in themes and findings.

Results

Results from the RCT will be analyzed in the fall of 2019 and be published in peer-reviewed journals in the fields of telerehabilitation, clinical cardiology, and health economics and be presented at international conferences.

The evaluation of the Future Patient Telerehabilitation program includes the clinical data recorded by the patient and psychosocial, health literacy, and eHealth literacy through questionnaires. Qualitative exploration of the perspectives of patients with heart failure, relatives, and health care professionals as well as a health economic evaluation will be conducted. The results from the RCT will be analyzed, and the results are expected to be published by spring 2020.

Discussion

Telerehabilitation Program

The aim of the Future Patient study is to test, implement, and evaluate a telerehabilitation program for patients with heart failure. The RCT was divided into three phases in the intervention group: a posthospitalization phase, a rehabilitation phase, and daily life adjustment 6 months after rehabilitation. A more holistic approach to patient rehabilitation is introduced on the basis of user-driven innovation, to accommodate the needs of the end user. This was just the first step toward engaging the patient in self-management. The uniqueness of this study lies in two areas: the use of a variety of self-monitoring methods and the use of SDT within a telerehabilitation context. The measurements include activity, pulse, and sleep trackers, which automatically transmit the monitored data to the HeartPortal. The HeartPortal has the potential to facilitate and educate patients in self-managing their disease. In this way, patients can become more engaged in their disease progression. The patient has the option of sharing their data, thus providing the patient's relatives the opportunity to monitor the progress of the patient through the HeartPortal, which, in turn, enables the relatives to motivate and support the patient according to their progression. The PRO data is a new tool that we will be tested, and we have not identified other studies that are working with PRO data for patients with heart failure.

The expected benefit of the health economy evaluation for the telerehabilitation group compared with the control group is increased quality of life, reduced contacts to outpatient clinics at the hospital, and a reduction in admissions to hospitals.

The HeartPortal is also designed to enable the patients to improve their eHealth literacy through a combined information platform. In addition, a communication platform has been incorporated into the HeartPortal, from which the patient and his/her relative can communicate with health care professionals, psychologists, and technical personnel. As such, the relative is an important member in this study, as studies have found that support from family and friends benefits patients with heart failure by improving patients' quality of life and reducing rehospitalizations [40]. Additionally, support from family and friends may promote self-management behaviors in the patient with heart failure, facilitating increased medication and dietary adherence [40].

Limitations

This study had three limitations that should be considered. First, a subject group consisting of patients with heart failure is highly sensitive to death, as this group is dominated by the elderly [40]. Second, the intervention period extends to 1 year and is therefore highly dependent on the sustained motivation of the subjects. Third, as the tracking devices used in the study are commercial products purchased for the purpose of automatically transmitting data to the HeartPortal, the study is highly dependent on the data transmission and access hereof. If the regulations for the devices change during the study period, it would be necessary to replace them with other devices, which may lead to inconsistency in biases.

Conclusions

The expected outcomes are increased quality of life, increased motivation and illness perception, reduced anxiety and depressions, improved eHealth literacy, and health economics benefits. We expect the study to have a clinical impact for future telerehabilitation of patients with heart failure.

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Conflicts of Interest

None declared.

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Abbreviations

eHealth: electronic health
eHLA: eHealth literacy assessment toolkit
eHLQ: and the eHealth Literacy Questionnaire
FPD: Future Patient database
HADS: Hospital Anxiety and Depression Scale
HCCQ: Health Climate Change Questionnaire
IPQ: Illness Perception Questionnaire
KCCQ: Kansas City Cardiomyopathy Questionnaire
NYHA: New York Heart Association
PRO: patient-reported outcomes
QoL: quality of life
RCT: randomized controlled trial
SDT: self-determination theory

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Protocol

Noninvasive Bimodal Neuromodulation for the Treatment of Tinnitus: Protocol for a Second Large-Scale Double-Blind Randomized Clinical Trial to Optimize Stimulation Parameters

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Abstract

Background: There is increasing evidence from animal and human studies that bimodal neuromodulation combining sound and electrical somatosensory stimulation of the tongue can induce extensive brain changes and treat tinnitus.

Objective: The main objectives of the proposed clinical study are to confirm the efficacy, safety, and tolerability of treatment demonstrated in a previous large-scale study of bimodal auditory and trigeminal nerve (tongue) stimulation (Treatment Evaluation of Neuromodulation for Tinnitus - Stage A1); evaluate the therapeutic effects of adjusting stimulation parameters over time; and determine the contribution of different features of bimodal stimulation in improving tinnitus outcomes.

Methods: This study will be a prospective, randomized, double-blind, parallel-arm, comparative clinical trial of a 12-week treatment for tinnitus using a Conformité Européenne (CE)–marked device with a pre-post and 12-month follow-up design. Four treatment arms will be investigated, in which each arm consists of two different stimulation settings, with the first setting presented during the first 6 weeks and the second setting presented during the next 6 weeks of treatment. The study will enroll 192 participants, split in a ratio of 80:80:16:16 across the four arms. Participants will be randomized to one of four arms and stratified to minimize baseline variability in four categories: two separate strata for sound level tolerance (using loudness discomfort level as indicators for hyperacusis severity), high tinnitus symptom severity based on the Tinnitus Handicap Inventory (THI), and tinnitus laterality. The primary efficacy endpoints are within-arm changes in THI and Tinnitus Functional Index as well as between-arm changes in THI after 6 weeks of treatment for the full cohort and two subgroups of tinnitus participants (ie, one hyperacusis subgroup and a high tinnitus symptom severity subgroup). Additional efficacy endpoints include within-arm or between-arm changes in THI after 6 or 12 weeks of treatment and in different subgroups of tinnitus participants as well as at posttreatment assessments at 6 weeks, 6 months, and 12 months. Treatment safety, attrition rates, and compliance rates will also be assessed and reported.

Results: This study protocol was approved by the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee in Dublin, Ireland. The first participant was enrolled on March 20, 2018. The data collection and database lock are expected to be completed by February 2020, and the data analysis and manuscript submission are expected to be conducted in autumn of 2020.

Conclusions: The findings of this study will be disseminated to relevant research, clinical, and health services and patient communities through publications in peer-reviewed journals and presentations at scientific and clinical conferences.

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International Registered Report Identifier (IRRID): DERR1-10.2196/13176

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KEYWORDS

tinnitus; bimodal; neuromodulation; trigeminal nerve; vagus nerve; auditory nerve; auditory cortex; pain; plasticity; precision medicine

Introduction

Tinnitus is the perception of sound in the absence of an external auditory stimulus and is commonly described as "ringing in the ears." The condition significantly affects approximately 5%-10% of the global population [1-3]. Tinnitus is heterogeneous, with a diverse range of etiologies, but is believed to be commonly accompanied by a sensorineural hearing loss [4-6]. One ongoing hypothesis is that the decreased input into the peripheral auditory system due to hearing loss causes spatial reorganization of the brain or compensatory changes in firing activity in multiple regions along the ascending auditory and nonauditory pathways that can lead to the tinnitus percept [3,5,7,8].

In individuals with normal hearing, sound travels as vibrations through the outer and middle ears into the cochlea, where cells within the cochlea convert the vibrations into neural signals that are transmitted along the auditory nerve to the brain [9,10]. The neural signals travel up through the brainstem, midbrain, and thalamus to the auditory cortex for sound perception. The ascending auditory pathway has a well-organized spatial map of frequencies (ie, neurons located in a certain region respond best to a specific sound frequency, and this spatial ordering of frequencies is known as tonotopy or a tonotopic map). In addition to the ascending pathway, there are dense descending connections from higher auditory and cognitive centers down to earlier stages of auditory neurons, which provide a way for sound perception to be modified or fine-tuned by attention and learning centers [11-16]. Furthermore, there are widespread projections from limbic and nonauditory pathways, such as somatosensory pathways, to the auditory network [17-27].

In tinnitus patients, the abnormal reorganization of the auditory brain can occur as spatial reorganization of the tonotopic map or changes in neural firing in one or several of the auditory regions [3,5,7]. For example, a high-frequency hearing loss could lead to a downregulation of peripheral synapses and activity in the high-frequency region of the thalamus (eg, medial geniculate body) and auditory cortex, in which those neurons then become more sensitive and active to lower frequency sounds (ie, an expanded frequency representation in the auditory brain for lower frequencies). Due to this frequency expansion and changes in firing patterns in those regions (eg, hyperactivity or hypersynchrony across neurons), the patient experiences a phantom percept (tinnitus) corresponding to that expanded brain region. There are recent studies suggesting that topographic reorganization may not be necessary for tinnitus or phantom sensations, in general [28,29]. It may be possible that the central auditory system broadly overcompensates for the loss of peripheral input and increases the central gain in different networks of neurons along the ascending auditory pathway. In connection with multiple nonauditory brain regions, this enhanced gain across the auditory network may not only cause excessive cortical activity and phantom sound awareness, but can also link and worsen the emotional and cognitive/memory attributes with the phantom percept [30,31].

The most commonly used approach for treating tinnitus is auditory stimulation, such as sound amplification (eg, hearing aids) or sound therapy (eg, noise maskers, tone sequences, or music therapy), which are intended to drive additional input into the auditory system and interact with the abnormal auditory neurons involved with tinnitus [32-36]. Based on extensive research in animals and several human studies, an emerging approach for driving strong plasticity and altering neurons within the auditory system is bimodal neuromodulation using acoustic stimulation combined with a nonauditory input, such as with vagus, somatosensory, or trigeminal nerve stimulation [20,37-45]. Since somatosensory or trigeminal inputs can activate or modulate neurons throughout the auditory pathway [20,23,24,27,46-52], combining sound stimulation with electrical stimulation of different body locations, especially via cranial nerves, has gained increasing interest as a promising approach for reversing the abnormal patterns of auditory neurons associated with tinnitus. Relevant to the proposed clinical study, experiments in animals have shown that combining sound stimulation with electrical stimulation of the tongue can drive extensive changes across the auditory system up to the midbrain and cortex that can potentially treat tinnitus, in which electrical stimulation of the tongue could drive greater auditory plasticity than stimulation of other somatosensory or trigeminal inputs [20].

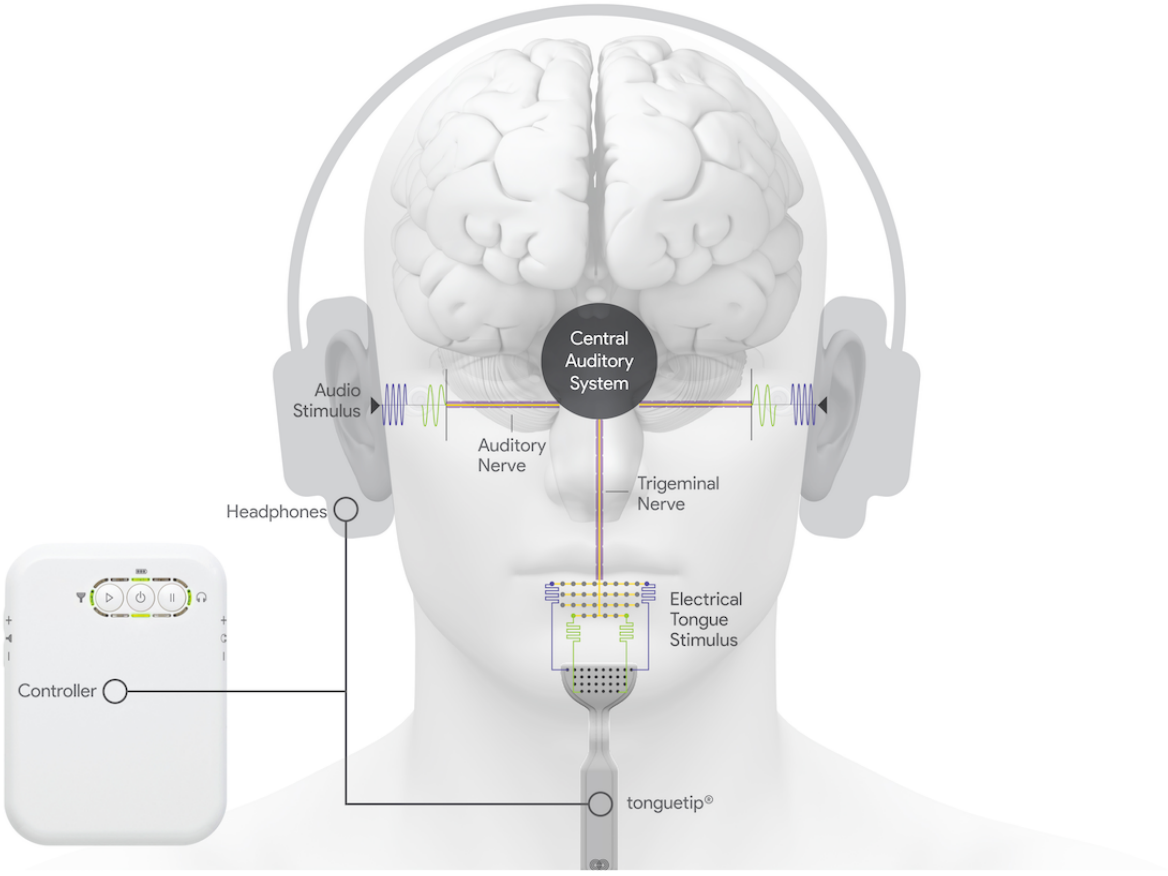
To date, there have only been a limited number of small and uncontrolled pilot studies to assess the safety and efficacy of bimodal neuromodulation approaches employing sound stimulation combined with cranial nerve stimulation for tinnitus treatment. These include invasive vagus nerve stimulation [41,53], noninvasive stimulation of the vagus nerve [54-56], and noninvasive cervical or trigeminal nerve stimulation [42-44,46,47]. Although the vagus nerve stimulation demonstrated promising results in animals [37], human studies have shown mixed results [41,53]. Published human studies using noninvasive cervical or trigeminal nerve stimulation have demonstrated promising initial efficacy [42-44]. However, these results should be considered preliminary, as the data stem from small pilot studies. Therefore, progression to properly designed,

sufficiently powered, blinded, randomized clinical trials are critically needed in the tinnitus field [34,36,57,58] to further confirm the efficacy and safety of bimodal neuromodulation combining sound and cranial nerve stimulation.

This study protocol is part of a major clinical development program sponsored by Neuromod Devices (Dublin, Ireland) to provide large-scale clinical evidence of the safety and efficacy of a new bimodal neuromodulation treatment for tinnitus (using acoustic and trigeminal nerve stimulation; Figure 1). This study protocol is designed to confirm and potentially enhance, through further stimulation optimization, the clinical efficacy demonstrated in a recently completed clinical trial (Treatment Evaluation of Neuromodulation for Tinnitus - Stage A1 [TENT-A1]) that evaluated bimodal neuromodulation in 326 tinnitus participants. The TENT-A1 protocol has been previously published [59]. TENT-A1 was a double-blind, two-site randomized study that evaluated the relative efficacy and safety of three different settings for acoustic and trigeminal stimulation (ie, settings related to acoustic frequencies and background noise, electrical stimulation patterns on the tongue with a 32-site surface electrode array, and intermodality delays). The treatment period was 12 weeks, wherein the therapeutic effects were assessed during treatment and at several follow-up visits up to 12 months posttreatment. Participants were presented with one stimulation setting for the entire 12-week treatment period. The positive results from TENT-A1 [60] have led to further questions and new directions for confirming and further optimizing stimulation parameters for bimodal neuromodulation, which will be investigated through the protocol presented in this paper describing a follow-up, double-blind, randomized clinical trial (Treatment Evaluation of Neuromodulation for Tinnitus - Stage A2 [TENT-A2]) in 192 participants with tinnitus.

The primary objectives of TENT-A2 are to (1) confirm the positive therapeutic effects, safety profile, and tolerability of treatment observed in TENT-A1; (2) determine the therapeutic effects of changing the stimulation parameters over time, in which the first stimulation setting is presented during the first 6 weeks of treatment and a second stimulation setting is presented during the next 6 weeks of treatment; and (3) assess how treatment outcome depends on the contribution of different acoustic or tongue stimuli not tested in TENT-A1. TENT-A2 also investigates the relative response of patient subtypes to the different treatment parameters. Building on the data collected in TENT-A1, this study will allow for the continued collection and analysis of safety data.

Figure 1. Bimodal sensory neuromodulation device (Lenire) for tinnitus treatment. The system developed by Neuromod Devices (Dublin, Ireland) consists of wireless high-fidelity circumaural headphones that deliver acoustic stimuli, a 32-site surface electrode array (tonguetip) for presenting electrical stimulus patterns to the anterior dorsal surface of the tongue, and a battery-powered controller that coordinates both stimulus modalities.



Methods

Trial Design

TENT-A2 is a prospective, single-site, parallel-arm, randomized, double-blind, comparative study investigating the safety and efficacy of four different treatment arms. The treatment will be evaluated for 12 weeks, during which different parameter settings will be delivered sequentially in the first and second 6-week segments of treatment (Table 1). Participant assessments will be performed at screening, enrollment (start of treatment), interim (after 6 weeks of treatment with the first stimulation setting), and end of treatment (after 6 weeks of treatment with the second stimulation setting). Posttreatment assessments will be conducted at the 6-week follow-up, 6-month follow-up, and 12-month follow-up (Table 2). TENT-A2 will be conducted at the Wellcome Trust-HRB Clinical Research Facility at St. James's Hospital in Dublin, Ireland. The protocol was independently reviewed and approved by Research Ethics Committees of the Tallaght University Hospital - St James's Hospital (Reference: 2018-03-List 9). The trial is sponsored by Neuromod Devices. Our reporting follows standard protocol items for clinical trials defined in the SPIRIT 2013 Statement [61].

Table 1. Stimulation parameter settings that will be utilized for the four parallel treatment arms of the TENT-A2 study. Two different stimulus settings will be used for each treatment arm during the first and second 6-week periods of the 12-week treatment. Parameter setting (PS) labels listed in the table are specific names used internally in the company. PS1 is a stimulus setting equivalent to the one used in the previous TENT-A1 study to assess repeatability of results between two different studies. PS1 consists of a sequence of tones mixed with structured wideband noise, in which the tones are synchronized in time with electrical pulses presented to the tongue (for further details, see published protocol paper for TENT-A1 [59]). One or more acoustic or electrical features in PS1 are modified or removed to create the other proprietary stimulus settings used in the TENT-A2 study. A general description of the different stimuli is included in the table to sufficiently understand the rationale of the study design but without fully revealing the specific stimulation algorithm for each arm.

Treatment	First 6 weeks	Next 6 weeks
Arm 1	PS1[a]: Same stimulation setting used in Arm 1 of TENT-A1[b] for comparison of findings with TENT-A2[c]. A wide range of pure tones (0.5-7 kHz) are presented binaurally with each tone synchronized in time with an electrical pulse train that is presented to specific locations on the tongue via the 32-site tonguetip component. A background wideband noise is also mixed in with the stimuli. Presentation rate of each paired stimuli is approximately 12.5 Hz.	PS4: Similar to PS1, except that a randomly varying short delay (0-30 ms) is introduced between the tone and tongue stimuli, and the location of stimulation on the tongue is randomized across stimuli. PS4 is designed to investigate if a different stimulation setting from PS1 can drive additional therapeutic effects beyond the plateau effects observed for PS1 in TENT-A1.
Arm 2	PS6: Low-frequency pure tones (0.5-1 kHz) are presented binaurally with randomly varying long delays (~1 s) between each tone and tongue stimuli, in which the location of stimulation on the tongue is randomized across stimuli. Background noise is not included in PS6. Presentation rate is approximately 0.5 Hz. PS6 is designed to determine if specific features of PS1 are required for improvements in tinnitus symptom severity, in which TENT-A2 is powered to detect a clinically meaningful difference between PS1 and PS6.	PS10: Similar to PS4, with the main difference involving the use of a wideband noise instead of pure tones for the sound stimulus. PS10 is designed to investigate the efficacy and tolerability of tongue stimulation with a noise stimulus instead of pure tones.
Arm 3	PS7: Similar to PS6, except that the sound stimuli consisted of multiple simultaneous tones instead of single tones. PS7 is designed to investigate if broader spectrum tonal stimuli can drive additional therapeutic effects compared to PS6.	PS4: See description for PS4 above. PS4 is introduced in Arm 3 to allow for comparison with PS4 in Arm 1 and to assess if different stimulation settings during the first 6 weeks affect the therapeutic effects observed during the next 6 weeks.
Arm 4	PS9: Acoustic-only condition with same stimuli as PS6 but without tongue stimulation.	PS6: See description for PS6 above. The tonguetip is provided for tongue stimulation to investigate the therapeutic effects of bimodal stimulation compared to acoustic-only stimulation and to provide participants with a stimulation setting that is expected to improve tinnitus during the 12-week treatment period based on findings from TENT-A1. Therefore, participants in Arm 4, as with the other arms, are informed that they are randomly allocated to a treatment arm to maintain blinding (ie, all participants know they are receiving treatment and they do not know which treatment arm is supposed to include the most effective settings).

[a]PS: parameter setting.

[b]TENT-A1: Treatment Evaluation of Neuromodulation for Tinnitus - Stage A1.

[c]TENT-A2: Treatment Evaluation of Neuromodulation for Tinnitus - Stage A2.

Table 2. Schedule of visits, tasks, and assessments for TENT-A2 study.

TENT-A2[a] timeline	Screening	Enrollment and fitting	Post-allocation				Follow-up		
			Telephone call	Interim visit	Telephone call	Endpoint visit			
	t – 8 wk	t = 0 wk	t + 3 wk	t + 6 wk	t + 9 wk	t + 12 wk	t + 18 wk	t + 38 wk	t + 64 wk
Task									
Eligibility screen	✓								
Informed consent	✓								
Allocation		✓							
Training on using the device		✓							
Review of device usage data				✓					
Encourage subject compliance		✓	✓	✓	✓				
Return device						✓			
Intervention									
Arm 1		✓	✓	✓	✓	✓			
Arm 2		✓	✓	✓	✓	✓			
Arm 3		✓	✓	✓	✓	✓			
Arm 4		✓	✓	✓	✓	✓			
Assessment									
Medical history	✓					✓			
Medications or illnesses	✓	✓		✓		✓	✓	✓	✓
Audiometric test of hearing	✓					✓			
Tinnitus location and tonality	✓	✓		✓		✓	✓	✓	✓
Tinnitus loudness matching	✓								
Loudness discomfort level	✓	✓		✓		✓	✓	✓	✓
Mini-Mental State Examination	✓								
State-Trait Anxiety Inventory	✓								
Somatic assessment		✓							
Oral assessment		✓				✓			
Minimum masking level	✓	✓		✓		✓	✓	✓	✓
Pittsburgh Sleep Quality Index	✓	✓		✓		✓	✓	✓	✓
Tinnitus Handicap Inventory	✓	✓		✓		✓	✓	✓	✓
Tinnitus Functional Index	✓	✓		✓		✓	✓	✓	✓
Visual analogue scales	✓	✓		✓		✓	✓	✓	✓
Hyperacusis questionnaire		✓		✓		✓	✓	✓	✓
Clinical Global Impression				✓		✓	✓	✓	✓
Adverse Events	✓	✓		✓		✓	✓	✓	✓
Device usability questionnaire						✓			
Demographic data							✓		

[a]TENT-A2: Treatment Evaluation of Neuromodulation for Tinnitus - Stage A2.

[b]t: timepoint from enrollment and fitting.

Eligibility Criteria

Eligible participants will be aged 18-70 years at screening, self-report experiencing predominantly tonal tinnitus for >3 months and <10 years, score 38-100 points on the Tinnitus Handicap Inventory (THI), have a wide-band noise Minimum Masking Level (MML) measurement between 20 and 80 dB hearing level (HL), be able to read and understand English, be willing and able to provide informed consent, and be willing to commit to the full duration of the study. Participants with predominantly tonal tinnitus (not atonal tinnitus) will be recruited to simplify the study design and analyses to a less diverse and heterogeneous group. In the TENT-A1 study, participants with tinnitus lasting for 3 months up to 5 years were recruited. The same lower boundary will be used in the TENT-A2 study, in which the Sponsor and its Scientific Advisory Committee originally considered 3 months as the start of transition from acute to chronic tinnitus. The upper boundary was increased to 10 years to enhance recruitment within a shorter period of time than that in the TENT-A1 study.

Candidates will be excluded if they have objective tinnitus; pulsatile tinnitus (rhythmical sounds that often beat in time with the heartbeat); somatic tinnitus caused by a head or neck injury; or tinnitus that is comorbid with a neurological condition that may lead to loss of consciousness or is considered to be the dominant feature of the tinnitus, as assessed by an audiologist or clinician. Abnormal otoscopy or abnormal tympanometry, as possible indicators of conductive hearing loss, are exclusion criteria, as is a sensorineural hearing loss either unilaterally or bilaterally, wherein the subject has >40 dB HL in at least one measurement frequency in the range of 0.25-1.00 kHz or has >80 dB HL in at least one measurement frequency in the range of 2.0-8.0 kHz. In addition, we will also exclude participants who began wearing a hearing aid within 90 days prior to eligibility assessment, those with any type of electroactive implantable device (eg, vagal nerve stimulator, cochlear implant, or a cardiac pacemaker) and those with the following conditions that can be comorbid with tinnitus: Meniere's disease, loudness discomfort level for sounds presented <30 dB sensation level, temporomandibular joint disorder, and psychological conditions determined by a score >120/160 on the State-Trait Anxiety Inventory (STAI) [62,63]. Moderate to severe dementia, as indicated by a score <20 on the Mini-Mental State Examination (MMSE) [64], will also be a sufficient reason for exclusion. A final set of exclusion criteria based on medical history taken at the screening assessment include oral piercings, pregnancy, involvement in medicolegal cases, history of auditory hallucinations, current prescription of a drug for a central nervous system pathology (ie, epilepsy, multiple sclerosis, Parkinson disease, and bipolar disorder), and previous use of a Neuromod Devices product. Finally, the participant may be excluded if the principal investigator does not deem the candidate suitable for the study for reasons not listed above.

Intervention

Participants enrolled in the trial will be given a proprietary Conformité Européenne (CE)-marked Class IIa medical device, which comprises bimodal auditory and trigeminal nerve (tongue) stimulation from the sponsor company (Figure 1; Neuromod Devices, Dublin, Ireland). High-fidelity Bluetooth headphones deliver the auditory stimulation, which includes sequences of pure tones and wideband noise. The trigeminal nerve is stimulated electrically via a 32-electrode transmucosal array placed on the anterior dorsal surface of the tongue. Tongue stimulation is delivered in the form of biphasic anodic-leading pulses of duration between 5 and 130 μs and fixed amplitude. The electrodes in the array are stimulated in a temporospatial pattern that represent features of the acoustic stimulus, such as the frequencies and onset of stimulus tones. Each stimulation parameter setting (PS) listed in Table 1 represents a different combination of acoustic and tongue stimulation patterns or delays that are being evaluated in this study. For example, PS1 and PS6 are used in the first 6 weeks of Arms 1 and 2, respectively, to allow comparison of an effective treatment setting from the TENT-A1 study (ie, PS1) with another bimodal condition (ie, PS6) to identify specific bimodal stimulation features for improving tinnitus symptom severity. The TENT-A2 study has been powered to detect a clinically meaningful difference between PS1 and PS6 during the first 6-week period. Additional stimuli listed in Table 1 and comparisons described in the Statistical Methods section have been included to achieve the main objectives of this TENT-A2 study. Further details and rationale for the different stimulation settings used within each treatment arm are provided in Table 1. Note that the current CE-marked 32-site electrode array (the tonguetip shown in Figure 1) has been successfully used for stimulation of the tongue to improve tinnitus symptom severity in the TENT-A1 study [60] and is used in this TENT-A2 study to further investigate the contribution of different stimulus features on therapeutic outcomes, as described in Table 1. In future studies, the minimum number of electrodes on the tongue required for sufficient therapeutic effects can be investigated.

Each participant's pure-tone audiometric thresholds (in the range 0.25 to 8 kHz) will be captured at the screening visit and subsequently used to configure the intensity of the auditory stimuli, typically 10 dB sensation level or more above their hearing thresholds. The participant will be provided with an option to adjust the default auditory stimulus intensities from –12 dB to +12 dB in 2-dB increments during treatment. For safety reasons, the upper level of stimulus intensity is limited for participants with >70 dB HL hearing loss at any frequency. The treatment device reverts to the default stimulus intensities at the start of each new treatment session. Any adjustments made by the participants to the stimulus intensities are logged in the device's memory for subsequent analysis.

The tongue stimulus intensity will be configured for each participant at enrollment, based on a calibration procedure that determines the participant's threshold of perception and sets the intensity at a suprathreshold and comfortable level. During treatment, the participant is also provided with the option to adjust the tongue stimulus intensity up to a maximum of 60% above the calibrated level or down to a minimum of 40% below the calibrated level, to allow participants to adjust for natural variances in somatosensory or perceptual sensitivity (eg, due to variations in electrolyte concentrations in the saliva or relative dryness in the mouth).

Participant usage and stimulus adjustments are logged automatically by the device, such as the time and date when the device is in use, the duration of electrode contact with the tongue, and the intensities of both the auditory and tongue stimuli.

Each device will be programmed with the personalized settings and treatment arm for each subject at the sponsor's manufacturing site. The devices will be clearly identified with the participant's unique identifier code (UIC). Investigators are extensively trained on fitting the device and instructing participants on its use per the manufacturer's instructions. Participants will be provided with a training session on how to use the device at the enrollment visit. A *Quick Start Guide* and a *User Manual* will be provided to each participant to take home. Before leaving the clinical site at the enrollment visit, participants will complete a supervised treatment session that is at least 15 minutes in duration, to ensure that they are competent and comfortable using the device.

Outcome Measures

Subjective clinical outcome measures commonly used to assess tinnitus symptom severity are the THI [65] and the Tinnitus Functional Index (TFI) [66,67]. The THI provides a measure of the emotional and functional impact of tinnitus, in which 25 items are scored 4/2/0 on a categorical scale corresponding to yes/sometimes/no, respectively. The global score of the THI has a value from 0 to 100, with a higher score indicating a greater negative impact of tinnitus. The TFI assesses a range of tinnitus-related functional complaints experienced over the week prior to assessment. Each of the 25 items is assessed on an 11-point Likert scale, and the sum of the scores is normalized to yield a global score of 0-100, with a higher score also indicating a greater negative impact. The Clinical Global Impression (CGI) is assessed at multiple visits to give an overall impression of the change in tinnitus (CGI-I) or sleep (CGI-S) since beginning treatment.

Tinnitus loudness is assessed by MML, tinnitus loudness matching (TLM), and a visual analogue scale (VAS). MML is a psychoacoustic estimate of the lowest level of wideband noise required to minimally mask the participant's tinnitus [68]. The stimulus is presented binaurally, after the participant's noise threshold level is obtained. TLM is assessed by presenting a 1-kHz tone contralateral to the predominant tinnitus ear or if tinnitus is equally loud in both sides or localized in the head, the stimuli are presented to the ear with better hearing [69]. The stimulus is increased until the participant confirms that it is equal in loudness to their tinnitus. TLM is only measured at screening. A VAS is employed for participants to rate the current loudness (or annoyance) of their tinnitus with 0 indicating "not loud at all" and 10 indicating "extremely loud" [70]. Both investigator-administered (MML and TLM) and participant-reported assessments (VAS) are used, because there is no agreed standard for assessing tinnitus loudness. Although a tinnitus loudness rating performs better against acceptability criteria for reliability and validity than a TLM or MML test, the rating question is limited because it is a single-item instrument and is probably able to detect only large changes [71].

Participant-reported and investigator-reported adverse events (AEs) will be recorded, classified, coded, and summarized. AEs will be classified according to severity, causality, and whether they are anticipated. They will be further coded by type for subsequent analysis, trending, and reporting purposes. Any treatment-related serious AEs will be reported to the local competent authority, the Research Ethics Committee, and the sponsor's notified body, as required by local reporting regulations (in accordance with MEDDEV 2.12-1). The investigators will remain vigilant for signs of possible treatment-related changes in oral health (eg, irritation or discomfort in the oral cavity) and the impact on tinnitus.

Nonparticipant facing investigators will monitor the participants at the 6-week assessment, and the study may be stopped if the mean change in THI increases by 7 points and that in TFI increases by 13 points, or if the mean change in MML increases by 5.3 dB, in any treatment arm relative to enrollment values. Treatment-related changes in hearing thresholds that will be considered an AE is a deterioration from screening to the end of treatment of 15 dB in a minimum of two adjacent test frequencies (0.25-8 kHz) in either ear that cannot be explained by a conductive hearing problem or a recent excessive noise exposure and which continues at a subsequent follow-up visit. An additional safety endpoint will be that the mean change in hearing thresholds across all participants does not worsen by more than expected due to age-related hearing loss.

Compliance data will be extracted from log files on each participant's device. The compliance rate will be expressed as a percentage of usage relative to the expected compliance as per the intended use for the device (a total of 42 hours over the 6-week period and a total of 84 hours over the 12-week period) and to a predefined minimum acceptable compliance threshold (defined as at least 3 hours of average usage within a 1-week period, corresponding to a sum total of 18 hours of treatment for the first 6-week period and 36 hours of treatment for the full 12-week period). This minimum acceptable compliance threshold is what was defined in the previous TENT-A1 study that still led to positive therapeutic effects for tinnitus treatment, and thus, a similar threshold is used in this study to enable comparison of results across studies.

Recruitment

Participants will be recruited primarily via regional and national radio advertising that directs participants toward a dedicated trial sign-up website [72]. The recruitment website provides information on the study and how to proceed with registration. To register their interest, candidates must enter their email address, so that they can be emailed a UIC and personal identification number as well as a link to an online eligibility assessment (hosted by SurveyGizmo). To access the online eligibility assessment, candidates must click the link, which brings them to a log-in page that requires them to input their UIC and personal identification number. Once logged in, candidates can find further details about the requirements of participating in the study. Candidates will answer a set of general prescreening questions on age, duration of tinnitus, oral piercings, other current medical conditions, and other eligibility criteria-related questions. The online eligibility assessment is

intended to reduce the burden of performing detailed screening visits on a large number of candidates who are expected to be interested in the trial, yet would not satisfy the inclusion and exclusion criteria. Candidates who meet the inclusion criteria will be provided with a participant information leaflet and informed consent form via email or post and invited to a screening visit at the Wellcome Trust-HRB Clinical Research Facility at St. James's Hospital in Dublin, Ireland.

Study Timeline

Participants will be expected to visit the clinic seven times throughout the entirety of the study. They will also receive two compliance telephone calls during the device usage period, one during the first 6 weeks and the other during the next 6 weeks of treatment. The schedule of clinical research activities is illustrated in Table 2. Various assessments will be completed by a multidisciplinary team including audiologists, medical doctors, physiotherapists, research nurses, and clinical investigators.

The screening visit will be used to determine whether a participant is eligible for enrollment into the trial, as defined by the abovementioned inclusion and exclusion criteria. The initial objective of the screening visit is to obtain written informed consent, in which the participants will be given sufficient time to read through the participant information leaflet and informed consent form. Initial outcome measure assessments, participant characteristics, and audiological profile are also obtained at the screening visit. This information is employed in the subgroup classification of participants, the stratified random allocation process, and for device configuration as described below.

At the enrollment (device fitting) visit, a physiotherapist will conduct a comprehensive assessment comprising a set of 25 predefined cranial manipulations designed to diagnose somatic tinnitus [26] as well as five additional maneuvers of the tongue. In this study, somatic tinnitus is defined as tinnitus where at least one of the somatic manipulations reliably produces a change in any psychoacoustic characteristics of a participant's tinnitus (eg, in pitch, loudness, or localization). Assessments of outcome measures previously assessed at the screening visit are repeated at the enrollment visit. The enrollment visit also entails an oral health examination, device training and deployment, and a supervised treatment session. The treatment is self-administered by the participant daily for two 30-minute sessions over the course of the treatment. These sessions can be contiguous or completed at different times of the day.

The outcome measure assessments and safety information collection are repeated at the interim visit, halfway through the 12-week treatment. Compliance data will also be assessed and reviewed at the interim visit. Participants with poor compliance will be encouraged to improve their treatment device usage.

The assessments will be repeated at the endpoint visit (ie, end of 12-week treatment), including the outcome measure assessments and the oral health examination. An exit interview will be completed and the device will also be retrieved at the endpoint visit. Three follow-up visits will then be conducted to assess the posttreatment effects of the intervention. These posttreatment assessments will be conducted at the 6-week follow-up, 6-month follow-up, and 12-month follow-up, as listed in Table 2.

Sample Size

Arm 1 and Arm 2 are powered to detect a between-arm clinically meaningful difference in the mean THI changes from enrollment to interim, where the clinically meaningful change in THI is considered to be 7 points [73]. The assumed sample standard deviation is 12 points, as estimated from a previous study sponsored by Neuromod Devices (TENT-A1) [60]. The sample size calculations were performed using Matlab 2016a (MathWorkds, Natick, Massachusetts), assuming a two-sided significance level of 0.025 (pairwise *t* test) and power of 90%, resulting in a total of 75 participants to be enrolled in treatment Arms 1 and 2. The remaining 0.025 of the overall 0.05 significance level is retained for within-arm and subgroup hypothesis tests.

Arms 3 and 4 are included for exploratory endpoints and are powered to detect a between-arm 10-point THI difference compared to Arm 1 from enrollment to interim. This requires approximately 15 participants in Arm 3 and Arm 4. Therefore, the allocation ratio among treatment arms is 5:5:1:1. In total, 180 participants (75+75+15+15) will be required to complete the interim assessment (first 6 weeks of treatment) across the four arms of the study. The attrition rate for the first 6 weeks of treatment in TENT-A1 was approximately 7%. Therefore, it is estimated that approximately 193 participants would need to be enrolled to ensure 180 participants complete the 6-week treatment assessment. This number is rounded down to 192 participants to ensure a balance at the required ratio (5:5:1:1 in Arms 1, 2, 3, and 4).

Allocation

Eligible participants will be randomized as per the allocation ratio previously described (5:5:1:1) between the four parallel treatment arms (Table 1). Stratified randomization using the method of minimization [74] will be performed to balance the influence of several baseline covariates in the posthoc analyses. The stratification covariates are chosen based on the investigator's research objective to elucidate relative treatment effects on possible subtypes of tinnitus participants with varying underlying characteristics. Allocation of participants will be stratified across the four intervention arms based on findings from TENT-A1 and in ranked order as per the following strata: (i) hyperacusis <70 dB sensation level at 500 Hz, (ii) hyperacusis <60 dB sensation level at 500 Hz (note that the loudness discomfort level assessment is used as an indicator for hyperacusis at screening), (iii) high THI of >56 points at screening, (iv) unilateral tinnitus as assessed at screening, and (v) participants who do not fall into the previous categories (note that this stratum will not be used to draw an inference).

Data Collection

All data will be collected electronically using a validated electronic clinical case report form (eCRF) application. Participant data collected at all stages of the trial will be entered into the eCRF using UICs assigned to participants at recruitment phase. All participants and investigators performing the

participant evaluations will be blinded to the allocation arm, and no allocation information will be contained in the eCRF. The data monitors will be able to remotely view the blinded data in the eCRF to monitor safety data.

Statistical Methods

The primary efficacy analyses will focus on investigating: (1) within-arm (Arm 1) changes in THI and TFI from baseline (average of screening and enrollment) to interim (first 6 weeks of treatment) and (2) between-arm (Arm 1: Arm 2) changes in THI from enrollment to interim. These comparisons will be performed for the full cohort of participants as well as two subgroups of participants (ie, one hyperacusis subgroup and a high tinnitus symptom severity subgroup). The statistical analyses for testing these hypotheses while accounting for multiple comparisons are depicted in Figure 2, which shows how all primary efficacy analyses will be controlled at an overall significance level of 0.05 using a graphics-based sequential/parallel testing procedure with fallback [75]. The between-arm calculations use values from enrollment to interim in order to assess improvements in tinnitus symptom severity across different stimulation settings relative to the actual start of treatment. The within-arm calculations are using values from baseline to interim to match the design of the previous TENT-A1 study in order to allow direct comparison of findings across studies, which is one of the main objectives of this TENT-A2 study. The rationale for investigating the within-arm and between-arm changes for the hyperacusis subgroup (loudness discomfort level <70 dB sensation level at 500 Hz at screening) and the high tinnitus symptom severity subgroup (THI >56 points at screening), as well as stratifying the participants across treatment arms based on these subgroups, is that greater improvements in tinnitus symptoms from bimodal neuromodulation were observed for individuals with greater hyperacusis or tinnitus symptom severity in the TENT-A1 study. Analyses of these subgroups were not prespecified as primary efficacy endpoints in TENT-A1, and therefore, they are included in the primary efficacy endpoints for this TENT-A2 study.

The between-arm analyses will be based on an intention-to-treat estimand tested with multiple regression using enrollment scores as a covariate. Missing data will be handled by using Markov chain Monte Carlo multiple imputation methods [76,77]. The within-arm analyses will be based on a per-protocol estimand and tested with paired two-tailed *t* tests. The use of per-protocol estimand will ensure that the changes in outcome measures within each treatment arm are reflective of real-use scenarios, that is, where the participants use the treatment as directed. The threshold for inclusion in the per-protocol analysis is set at the predefined minimum acceptable compliance threshold previously described.

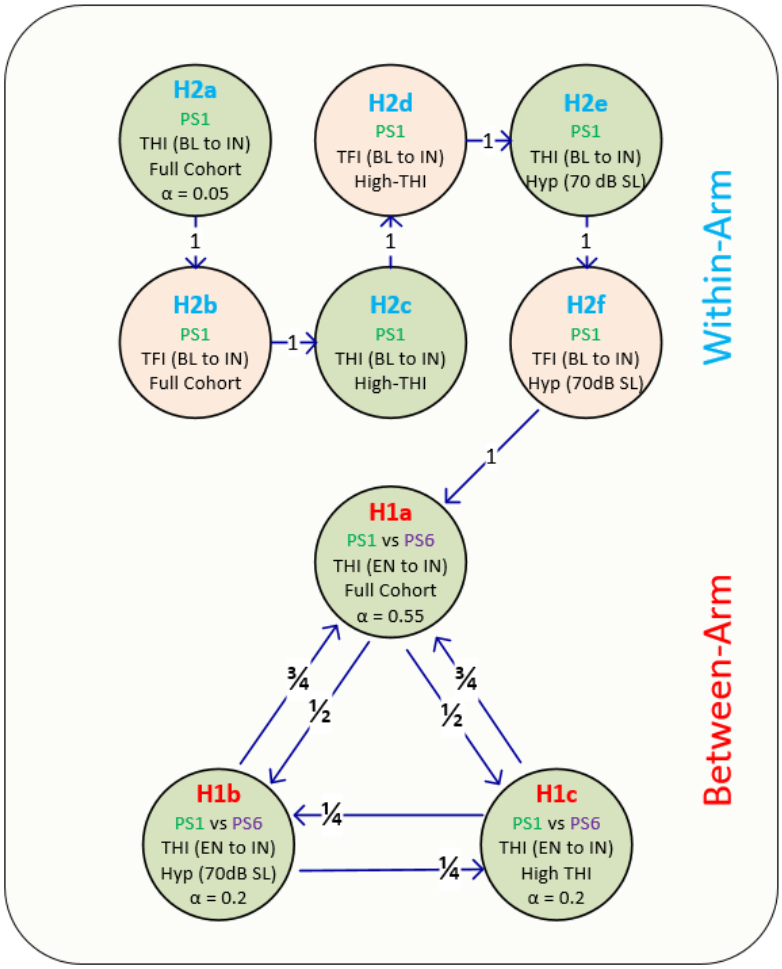
Additional efficacy analyses will be conducted to evaluate further improvements in the within-arm changes in THI from interim to the end of treatment due to the use of different stimulation settings over time, therapeutic effects in different subtypes of tinnitus participants described previously, and sustained effects by analyzing changes in efficacy outcome measures from the end of treatment to the three follow-up assessments (ie, at 18, 38, and 64 weeks after device fitting). Similar assessments performed for THI will be performed for TFI as additional analyses.

As shown in Figure 2, there are specific hypotheses that will be tested in this study and controlled at an overall significance level of .05. However, as listed in Table 1, several different stimulation settings have been included with the intent of comparing treatment effects between settings and across different time points. Due to limited resources, it is not possible to recruit enough participants to test all of our desired hypotheses or questions. Nevertheless, we will still analyze the data to identify trends that may be further evaluated in a follow-up confirmatory clinical trial. Several key aims that have been purposely incorporated into the design of the study are as follows: (1) to confirm similar within-arm changes in THI and TFI for PS1 in the TENT-A2 study, as observed in the TENT-A1 study for the first 6-week period; (2) to investigate the effect of changing the stimulation settings from PS1 to PS4 in Arm 1, in which a plateau effect was observed after the first 6-week period in the TENT-A1 study when using the same stimulation setting (ie, PS1) for the entire 12-week period; (3) to assess if bimodal stimulation with specific or complex pure tones (without wideband noise) is sufficient to drive therapeutic effects or if inclusion of wideband noise (or wideband noise alone) is required for improving tinnitus symptom severity with bimodal stimulation in Arm 2 and Arm 3; (4) to investigate if bimodal stimulation achieves greater improvements in tinnitus symptom severity compared to acoustic stimulation alone; and (5) to assess the long-term therapeutic effects (up to 12 months after end of treatment) of different stimulation settings across treatment arms and in comparison with the sustained effects observed in the TENT-A1 study. All four treatment arms are considered to be blinded to the participants, because each participant is informed that they are receiving a bimodal neuromodulation treatment during a 12-week period and they do not know which treatment arm consists of the most effective stimulation settings.

Safety analyses will be performed by evaluating the incidence and expectedness of AEs, classified as treatment or nontreatment related and further subclassified according to severity. AEs will be recorded proactively by monitoring significant deteriorations in THI, TFI, MML, hearing thresholds, and oral health and reactively by documenting any AEs reported by participants during the study. All AEs will be analyzed for trends.

Efficacy and safety data analyses will be conducted in compliance with the Consolidated Standards of Reporting Trials guidelines for randomized trials [78].

Figure 2. Hypothesis testing accounting for multiple comparisons. The primary endpoints for the TENT-A2 study correspond to several parallel and serial hypotheses depicted in the figure. A *P* value of .05 is initially distributed across four hypotheses (H1a, H1b, H1c, H2a), in which the portion of the *P* value attributed to each hypothesis is indicated by the alpha value. For example, alpha equals 0.55 for H1a, which corresponds to the null hypothesis being rejected if *P*<.0275 (.55x.05). The null hypothesis for H1a is that there is no between-arm difference in changes in mean Tinnitus Functional Index score from enrollment to interim (6-week timepoint) between parameter setting (PS) 1 and PS6 for the full cohort of participants. The null hypothesis for H1b and H1c is that there is no between-arm difference in changes in mean THI score from enrollment to interim between PS1 and PS6 for the hyperacusis subgroup and high tinnitus symptom severity subgroup, respectively. Both are rejected if *P*<.01 (.2x.05). The null hypothesis for H2a is that there is no within-arm change in THI from baseline (average of screening and enrolment scores) to interim for the full cohort of participants. H2a is rejected if *P*<.0025 (.05x.05). Note that the remaining hypotheses (H2b, H2c, H2d, H2e, H2f) can only be tested if the previous hypothesis in the series is rejected. For example, if H2a is rejected, then its portion of the *P* value (*P*=.0025) is transferred to H2b for testing. If H2b is rejected, then its portion of the *P*> value (*P*=.0025) is transferred to H2c, and so on. Similarly, the arrows shown for the between-arm comparisons indicate that if any of the other hypotheses (for H1a, H1b, or H1c) are successfully rejected, then their portion of the *P* value is distributed to its neighbors based on the proportion labeled on each arrow. The null hypothesis for the within-arm comparisons (H2a to H2f) is that there is no within-arm change in THI or Tinnitus Functional Index from baseline to interim for the full cohort of participants, hyperacusis subgroup, or high tinnitus symptom severity subgroup. Note that all within-arm comparisons will be based on a two-sided paired (dependent) t test, while all between-arm comparisons will be based on a linear regression with independent variables of treatment arm and THI score at enrollment. Further details on the statistical analysis plan are provided in the Statistical Methods section. BL: baseline, EN: enrollment, IN: interim, Hyp: hyperacusis subgroup (loudness discomfort level <70 dB sensation level at 500 Hz at screening), High-THI: high tinnitus symptom severity subgroup (THI >56 points at screening); TFI: Tinnitus Functional Index; THI: Tinnitus Handicap Inventory.



Results

The protocol was independently reviewed and approved by the joint Research Ethics Committee of the Tallaght University Hospital - St James's Hospital (reference: 2018-03-List 9). The trial was initially registered in ClinicalTrials.gov on May 8, 2018 (identifier: NCT03530306). The first participant was enrolled on March 20, 2018, with the last assessment planned for August 2019. The database is expected to be locked by February 2020, and the data analysis and manuscript submission are expected to be conducted in autumn of 2020. The findings will be distributed to relevant scientific, academic, clinical, health services and participant communities through publications in peer-reviewed and high-impact scientific journals as well as via seminars and talks at conferences.

Discussion

Overview

This paper outlines the protocol for a prospective single-site, parallel-arm, randomized, double-blind, comparative study designed to confirm the safety, efficacy, and tolerability of

bimodal neuromodulation for tinnitus treatment observed in the previous TENT-A1 trial as well as to determine the therapeutic effects of adjusting the treatment stimulation settings over time and to identify responsive subtypes of tinnitus participants.

This study is important for the tinnitus field for several reasons. First, the findings in TENT-A2 can be compared to those obtained in TENT-A1 in order to assess if the safety and efficacy of bimodal neuromodulation treatment for tinnitus can be confirmed. Replication of clinical trial results is critically needed to build confidence in a field that is currently plagued with skepticism toward new types of treatment methods. Second, there are still only a few large-scale, blinded, randomized clinical trials for tinnitus treatment in which low-quality clinical trial design and reporting have been identified as a major barrier to developing effective therapies [58,79,80]. This study will not only provide valuable insight into the safety and efficacy for different parameter settings of bimodal neuromodulation for tinnitus participants but will also contribute to the establishment of higher clinical standards for evaluating different tinnitus treatments than are currently practiced. Third, there is a movement in the clinical realm toward personalized medicine and optimizing treatments per patient. The design of this study may reveal specific stimulation features and temporal effects of treatment for driving greater improvements in tinnitus in different subtypes of patients and will help move the field toward more reliable treatment outcomes.

Strengths and Limitations

The main strength of this study is that it is a large, double-blind, randomized clinical trial designed to confirm the safety, efficacy, and tolerability of treatment demonstrated in a previous large, double-blind, randomized clinical trial. Building on the previous trial, this study will further inform our understanding of the contribution or necessity of different sound and tongue stimulation parameters on the clinical efficacy of bimodal stimulation for tinnitus treatment. This study will comprehensively assess the therapeutic effect of different stimulation parameters in predefined patient subgroups that will refine candidature and improve personalization for the intervention in tinnitus patients, in which there are very few large-scale treatment studies providing such subtyping data in the tinnitus field.

A limitation of the study design is that the efficacy due to stimulation settings used during the second 6 weeks of treatment may not be directly comparable with efficacy due to the stimulation settings in the first 6 weeks of treatment because of possible carry-over effects. The cumulative effects from both stimulation settings used in each treatment arm can still be compared between arms to achieve one of the main objectives of the study.

Conflicts of Interest

BC, CH, SH, EM, and HHL have financial interest and/or are employed by Neuromod Devices Limited. DAH, SV, and BL serve on the Scientific Advisory Board of Neuromod Devices Limited and receive financial compensation for their services to the company.

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Abbreviations

CE: Conformité Européenne
CGI: Clinical Global Impression
HL: Hearing Level
MMSE: Mini-Mental State Examination
MML: minimum masking level

STAI: State-Trait Anxiety Inventory
TENT-A1: Treatment Evaluation of Neuromodulation for Tinnitus - Stage A1
TENT-A2: Treatment Evaluation of Neuromodulation for Tinnitus - Stage A2
TFI: Tinnitus Functional Index
THI: Tinnitus Handicap Inventory
TLM: tinnitus loudness matching
UIC: unique identifier code
VAS: visual analogue scale

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Protocol

The Effectiveness of Educational Mobile Messages for Assisting in the Prevention of Early Childhood Caries: Protocol for a Randomized Controlled Trial

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Abstract

Background: In 2017, approximately 3.7 billion downloads of health apps were made on mobile phones and tablets. In this sense, a massive number of people could benefit by electronic mobile–based health interventions, making information available even with the lack of material and human resources. Hence, the use of electronic apps for dental education might be extremely useful for the prevention of early childhood caries (ECC).

Objective: This study aims to evaluate the effectiveness of messages sent via mobile phones as an adjuvant method for the prevention of ECC.

Methods: A single-blinded, randomized, and parallel-group clinical trial will be conducted with dyads of parents or caregivers and children aged between 36 and 60 months, recruited from kindergartens and schools of Bauru, São Paulo. The determination of sample size resulted in a total of 104 dyads of parents and children, considering a power of 80%, a significance level of 5%, and an attrition of 30%. This sample will be randomly assigned to test and control groups, being divided in 52 dyads per group according to the health literacy levels of parents and the age, gender, and oral health status of children. Every 2 weeks, only participants in the test group will receive messages via WhatsApp containing preventive and education-related ECC information. The dyads will visit the dentist every 3 months during a year for the assessment of primary outcomes (sugar consumption and the International Caries Detection and Assessment System, visible plaque, and community periodontal indices) and to receive dental care measures. Secondary outcomes (electronic health literacy and general perceived self-efficacy) will be determined only at baseline and after 12-month follow-up. The quality of randomization will be evaluated throughout the study, comparing the test and control groups systematically by Student t tests for continuous variables and chi-square tests for categorical variables. Listwise deletion method will be applied in cases of dropouts, if the missing values satisfy the criteria of missing completely at random; otherwise, multiple imputation data strategy will be conducted. The Kolmogorov-Smirnov and Levene tests will be used to determine the normality and homogeneity of data, respectively, which will indicate further statistical analyses for elucidating significant differences between groups ($P<.05$). A Student t test or Mann-Whitney U test will be employed for parametric or nonparametric analyses, respectively.

Results: The project was funded in 2018, and enrollment was completed in August 2019. Allocation is currently under way and the first results are expected to be submitted for publication in 2020.

Conclusions: The results will contribute to understanding the importance of educational mobile messages toward the adoption of healthy behaviors for the prevention of ECC in a given population.

Trial Registration: Brazilian Registry of Clinical Trials Universal Trial Number U1111-1216-1393; http://www.ensaiosclinicos.gov.br/rg/RBR-2b6r7q/

International Registered Report Identifier (IRRID): PRR1-10.2196/13656

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KEYWORDS

eHealth; dental caries; randomized controlled trial

Introduction

Background

The unprecedented spread of electronic technologies has facilitated the access of internet users to health information [1-3]. In 2017, approximately 3.7 billion downloads of mobile health apps were made to be used on cellphones and tablets [4]. In this sense, a large number of people could be benefited by health interventions using mobile devices, providing information on health care even in situations of low availability of material and human resources [5]. Currently, WhatsApp Messenger (WhatsApp Inc.) is one of the most popular mobile apps worldwide, with approximately 300 million users [6]. It connects people through free electronic messages, requiring only a Wi-Fi internet network [7,8]. WhatsApp Messenger has been shown to be a promising tool for the communication between patients and professionals, aiding in the spreading of health-related information [9].

In this context, the use of electronic apps for dental education might be extremely useful for the prevention of early childhood caries (ECC). It is defined as the presence of one or more decayed, lost, or restored surfaces found in deciduous teeth of children aged up to 71 months [10]. This disease affects about 621 million children, positioning it as the tenth most prevalent chronic disease out of 291 conditions of Global Burden of Disease Study [11]. ECC causes the impairment of mastication and speech, pain, psychological problems, and negative effects on the weight and growth of children [12-14]. In addition, approximately 94% of children diagnosed with ECC develop carious lesions in permanent dentition [15]. The identification of individual risk factors, parental counseling, and health promotion have played an important role in the prevention of ECC [16], contributing to the improvement of the quality of life of children and their families.

Objectives

Therefore, new approaches are required to prevent ECC, aiming to improve the awareness about its consequences for deciduous and permanent dentitions, in addition to promoting the engagement of parents or caregivers with healthy behaviors toward the maintenance of oral health status of their children. In this sense, this study aims to assess the effectiveness of educational mobile messages sent via WhatsApp Messenger as an adjuvant method for the prevention of ECC in children of a given population. The null hypotheses for this study indicate that the educational mobile messages will not be effective for aiding in the control of dental plaque (H_0), the decrease of sugar consumption (H_0'), the maintenance of the International Caries Detection and Assessment System (ICDAS) indices (H_0''), and the improvement of parents' electronic health (eHealth) literacy levels (H_0''') after 12-month follow-up.

Methods

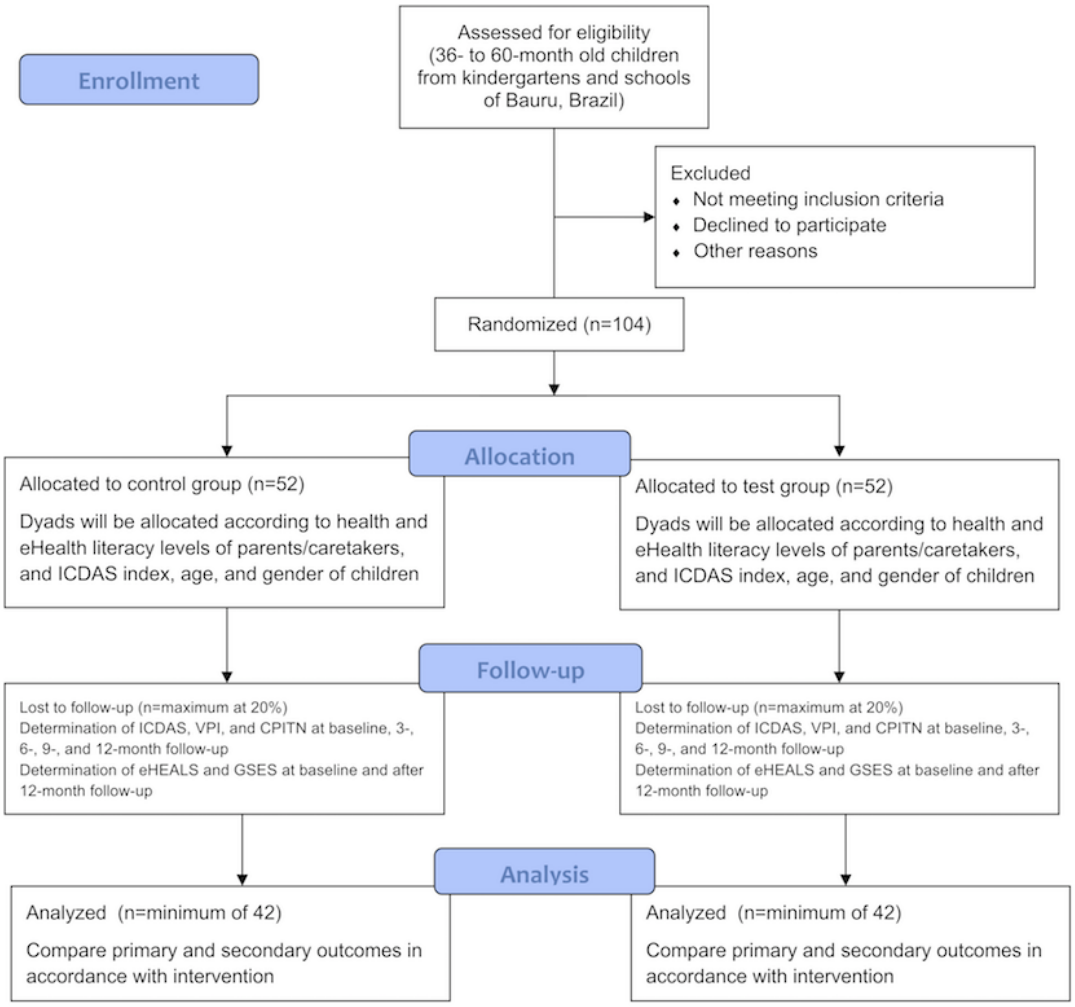
Overview

This study was reviewed and approved by the Council on Ethics in Human Research from the Bauru School of Dentistry (CAAE: 90563618.6.0000.5417), registered in the Brazilian Clinical Trials Registry (RBR-2b6r7q), and assigned with the universal trial number U1111-1216-1393. The peer review report is available in Multimedia Appendix 1.

Study Design

This protocol describes a single-blinded, parallel, and randomized controlled trial (RCT) that will analyze the effectiveness of educational mobile messages as an adjuvant strategy for the prevention of ECC. The messages will be periodically sent via WhatsApp Messenger to parents or caregivers of children, who will be recruited from kindergartens and schools of Bauru, Brazil. The participants will be randomly allocated to 2 different groups (test and control). This RCT will be conducted according to the checklist and guidelines of the Consolidated Standards of Reporting Trials of Electronic and Mobile Health (CONSORT EHEALTH; beta version 1.5) [17]. Figure 1 depicts the synthesis of the design of this study.

Figure 1. Study flowchart. CPITN: community periodontal index of treatment needs; eHealth: electronic health; eHEALS: The eHealth Literacy Scale; GSES: General Perceived Self-Efficacy Scale; ICDAS: International Caries Detection and Assessment System; VPI: visible plaque index.



Eligibility Criteria

Dyads of parents and children will be recruited during visits to kindergartens and schools located in Bauru, Brazil, if satisfying the following inclusion criteria: children aged between 36 and 60 months; children at high risk of dental caries, according to the criteria described in the Caries Risk Assessment Form for 0- to 5-Year Olds [18]; children with a score ≤3, according to the criteria of ICDAS [19]; parents or caregivers with a mobile phone with internet access; parents or caregivers who accept to participate in all stages of research by signing a written informed consent form; and parents or caregivers who already have WhatsApp Messenger app installed on their smartphones, or those who agree to install it for the participation in the study.

The risk of dental caries will be based on the information collected during the anamnesis and clinical examination, which will be performed by a trained and calibrated dentist. Children will be examined in a dental clinic, using compressed air and artificial lighting, following the ICDAS criteria [19], the visible plaque index (VPI) [20], and the community periodontal index of treatment needs (CPITN) [21].

The oral hygiene level of children will be determined by the observation of visible plaque on the buccal dental surfaces of 6 deciduous teeth (#55, #53, #51, #71, #73, and #75) [20]. The periodontal health status of children will be assessed considering 3 parameters of analysis: presence of bleeding, detection of dental calculus, and depth of gingival sulcus [21]. According to Almeida et al [22], this study will classify deciduous teeth with 1 of 3 different scores: healthy (0), gingival bleeding (1), and presence of dental calculus (2).

Electronic Health Literacy and Sociodemographic Questionnaire

The levels of eHealth literacy of parents or caregivers will be determined by the application of a previously validated Brazilian version of the eHealth Literacy Scale [23]. The eHealth Literacy Scale (eHEALS) will be applied by a trained professional, who provides the participants with a sheet containing 8 items related to skills needed to the adequate consumption of eHealth information. The answers of each item are arranged into a 5-point Likert scale, with options ranging from *completely agree* to *strongly disagree* [23]. The participants will be instructed to classify each item according to their own perception, achieving a total score varying from 8 to 40, with higher scores representing higher self-perceived eHealth literacy.

Finally, parents or caregivers will be invited to answer a questionnaire containing sociodemographic and child-related

health information such as age, gender, race, and education level.

International Caries Detection and Assessment System Training and Calibration

Overall, 2 investigators will be trained and calibrated for the use of ICDAS index according to the recommendations described below:

- An official trainer will make a 4-hour presentation, including images, discussions on ICDAS codes, and examination protocols.
- A total of 2 days of training will be given with the same number of teeth coded with ICDAS between 1 and 5, including the clinical examination of patients with decayed and extracted teeth.
- Examination findings will be reviewed to verify the repeatability of tests and differences in the interpretation until consensus among examiners.
- A total of 2 days of concordance evaluation will be performed, using at least 20 patients with dental caries lesions with ICDAS ranging from 1 to 5 (kappa>0.65) [19].

Randomization

Parent and child dyads will be randomly assigned to test or control groups, according to the parameters of stratification, as follows: health and eHealth literacy levels of parents or caregivers and the ICDAS index, age, and gender of children. The randomization will be performed using the platform Randomization.com [24], through different block sizes for the allocation of participants. The blinding of allocations will be guaranteed by using closed and opaque envelopes, which will be maintained confidential by an independent researcher.

Sample Size

The calculation of this sample size was performed using the Open Source Epidemiologic Statistics for Public Health, following the criteria and outcomes described by Zotti et al [25]. It resulted in a total of 104 dyads of parents and children, considering a power of 80%, a significance level of 5%, and an attrition of 30%.

Intervention

Every 2 weeks, the parents or caregivers of test group will receive educational mobile messages related to the prevention of ECC via WhatsApp Messenger. These materials will be developed by the researchers from the insights, including main doubts, questions, and challenges, regarding the disease, collected from the focus groups, conducted previously with the participation of a sample of parents or caregivers who attended the Clinics of Bauru School of Dentistry. These text messages will be formulated with a simple language for a better understanding, which will include emoticons and short and direct videos. The participants will be instructed to activate the function *read receipts* to confirm their adherence and engagement with the study. The participants' feedbacks related to the quality and utility of electronic messages for ECC prevention will be collected only after the 12-month follow-up, to avoid blinding biases.

All dyads of parents and children will be invited for dental appointments on a quarterly basis. The children will be examined by a trained and calibrated dental professional for the measurement of primary outcomes, receiving a subsequent dental prophylaxis. When necessary, fluoride varnish (Duraphat, Colgate) will be applied on dental demineralized surfaces (ICDAS=1 or 2), whereas a conventional glass ionomer cement (Ketac Molar Easymix, 3M) will be used for sealing localized enamel lesions (ICDAS=3). The investigators will not be informed about the origin of groups of participants, characterizing a single-blind study.

Sugar Consumption

A questionnaire developed by Llena and Forner [26] to investigate the dietary habits of dental patients will be applied at baseline and after the 12-month follow-up to evaluate the influence of sugar consumption on the development of oral diseases. The different types of food are divided into 9 categories: (1) foods containing sticky sugars: dried fruit, candies containing sugar, jellies, jams, and sauces; (2) foods containing starch and sugar: cookies, cereals, and industrialized cakes; (3) candy without sugars; (4) milk and dairy products containing sugar: chocolate, yogurt, creams, ice creams, and flans; (5) milk and dairy products without sugar: pure milk, sugar-free yogurt, and cheese; (6) sugary beverages: juices and soft drinks; (7) fruits: fruits and juices; (8) semihydrolyzed starch-rich foods: potato chips, French fries, industrialized bread, and rolls; and (9) sugar-free foods: nuts, bread, pasta, and noodles.

Study Outcome Measures

The primary outcomes will be related to the oral health status of children and the risk factors for ECC. For that, ICDAS, VPI, and CPITN indices will be determined for the recruitment of participants at baseline and 3-, 6-, 9-, and 12-month follow-ups.

The secondary outcomes will be related to the measurement of the influence of educative strategies on parents or caregivers, considering their patterns of sugar consumption, their level of eHealth literacy, and their individual perceptions about their own ability in executing specific activities. These data will be collected at baseline and after the 12-month follow-up using the questionnaire for sugar consumption [26], the instruments eHEALS [23], and General Perceived Self-Efficacy Scale (GSES) [27], respectively. In addition, the results of eHEALS will be applied for the recruitment of participants.

GSES measures the individual's beliefs about their cognitive, motivational, behavioral, and affective skills needed to perform particular tasks. It comprises 10 questions with answers arranged in a 4-point Likert scale, with options ranging from *not at all true* through *exactly true*. The total score ranges between 10 and 40 points, with greater scores indicating higher overall perceived self-efficacy of individuals [27].

Data Analysis

Statistical analysis will be performed using SPSS Statistics software 21.0 (IBM SPSS Statistics). The data will be presented with descriptive statistics, being examined for lost values, outliers, normality, and homogeneity. To investigate the quality

of randomization, potential differences between the characteristics of participants of the test and control groups will be determined systematically, applying Student *t* tests for continuous variables and chi-square test for categorical variables. Listwise deletion method will be adopted in cases of dropouts, if the lost values satisfy the criteria of the missing data completely at random; otherwise, multiple imputation data strategy will be used. The Kolmogorov-Smirnov and Levene tests will be used to analyze the normality and homogeneity of data, determining further statistical tests for detecting differences between groups ($P<.05$). A Student *t* test or Mann-Whitney *U* test will be employed for parametric or nonparametric analyses, respectively.

Results

At this moment, 104 dyads have already been recruited. The parents or caregivers have responded the questionnaires, while children are being examined to determine their baseline oral health status. From August, 2019, dyads will be allocated to control or test groups. The parents or caregivers will receive the first electronic message after 15 days of allocation. The first results related to oral health status of children are expected to be obtained in November, 2019. The data collection will be performed during 12 months, between August 2019 and 2020.

Discussion

Dental caries in deciduous teeth continue to affect the quality of life of children and their caregivers, regardless of their socioeconomic status, threatening the public health systems globally [28,29]. The prevalence of ECC ranges from 12% to 40%, with some developing regions reaching up to 98% [30,31]. Its incidence is approximately of 15,205 cases per 100,000 people, with millions of children diagnosed with the disease worldwide [11]. In 2016, the burden of untreated dental caries in deciduous teeth reached 6.59 disability-adjusted life-years for each 100,000 Brazilian preschoolers [32].

ECC is characterized by a multifactorial etiology, with a complex rampant progression that depends on the risk factors related to socioeconomic conditions such as low education levels, cariogenic diet, inadequate feeding practices, poor oral hygiene, and harmful daily habits under the responsibility of parents or caregivers [33-36]. The probability of the progression of this disease is high when there is no preventive or treatment interventions available [37]; however, the approach of treating ECC exclusively with dental restorative procedures is no longer considered appropriate. In this sense, the American Academy of Pediatric Dentistry recommends the following medical principles for controlling chronic noncommunicable diseases to reach better oral health outcomes [38,39] such as behavioral management focused on supplying specific needs of children and their caregivers [40]. Evidence supports a correlation of caregivers' low health literacy skills with inadequate child health status [41,42], weak disease resolution, lack of medication adherence [43,44], difficult-to-follow professional instructions [45], and lower medical visit rates [46]. Then, the limited capacity of parents or caregivers in comprehending materials containing essential knowledge for the prevention of ECC may impact directly on the outcomes of health education [41].

Parents and caregivers seem to play an important role in the management of chronic diseases of their children [47,48], especially when these diseases affect children under 3 years, which is observed with ECC. Mobile technologies have become important resources to empower patients to be active on their own conditions through shared decision-making process [49-52]. Nevertheless, parents and caregivers could be less used to electronic devices and even less to download apps for their mobiles or tablets [47,53]. Hence, ECC-related information delivered via WhatsApp Messenger could be an alternative to engage parents or caregivers in a healthy lifestyle, contributing to a better patient-professional relationship. This app is a low-cost instant-messaging platform very popular in Latin America, and more specifically in Brazil, where 56% of the population uses it frequently [54]. According to Ojeda et al [55], WhatsApp Messenger demonstrated its effectiveness for contacting patients, independently of their education level, making it a reliable source of information and an easy way for patient-professional interaction. A previous study reported a significant reduction of dental plaque in adolescents after using WhatsApp Messenger as an adjuvant for the prevention of oral diseases [56]. However, to our knowledge, there is no evidence showing the effect of educational electronic messages sent to parents or caregivers on the prevention of ECC.

These outcomes will demonstrate the influence of educational mobile messages sent via WhatsApp Messenger on the different parameters of oral health status of children, such as biofilm accumulation, dental demineralization, gingival health, and sugar consumption. In addition, the effect of this study protocol on the levels of eHealth literacy and perceived self-efficacy of parents or caregivers will be elucidated. All aforementioned analyses will consider the effect of possible sociodemographic confounding factors, after stratifying and controlling participants according to eHealth literacy levels of parents or caregivers and the ICDAS index, age, and gender of children.

The evidence produced in this study can support the development of digital strategies to be applied in ECC preventive programs, considering their 3 main advantages: scalability, cost-effectiveness, and empowerment of laypersons for self-dental care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from São Paulo Research Foundation.
[PDF File (Adobe PDF File), 84KB - resprot_v8i9e13656_app1.pdf]

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Abbreviations

CPITN: community periodontal index of treatment needs
ECC: early childhood caries
eHealth: electronic health
GSES: General Perceived Self-Efficacy Scale
ICDAS: International Caries Detection and Assessment System
RCT: randomized controlled trial
VPI: visible plaque index

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Protocol

The Use of Virtual and Immersive Technology in Creating Personalized Multisensory Spaces for People Living With Dementia (SENSE-GARDEN): Protocol for a Multisite Before-After Trial

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Abstract

Background: The number of people living with dementia is rapidly increasing. With dementia's impact on memory, communication, and self-identity, it is important to identify ways of meeting individual needs of diagnosed individuals and their caregivers. This study will test a new intervention, SENSE-GARDEN, that integrates autobiographical music, films, pictures, and scents with innovative technology to create an immersive environment tailored specifically for the individual.

Objective: The SENSE-GARDEN study is an Active Assisted Living Program–funded multicenter project. The primary objective of the study is to assess whether a personalized, innovative technology-based intervention can improve the well-being of older adults living with moderate to severe dementia. The study will also assess whether the intervention can improve coping and reduce burden in caregivers.

Methods: A controlled before-after study design will be used. There will be 3 sites in 3 trial countries: Belgium, Norway, and Portugal. A total of 55 people with dementia (PWDs) will be recruited. All eligible participants for the study will be randomized into the intervention or control group. For the first three months of the study, all participants will receive the SENSE-GARDEN intervention. For the final month of the study, the intervention group will continue visits to the SENSE-GARDEN, and the control group will discontinue visits. A mixed-methods approach will be used, including the use of standardized outcome measures, quantitative physiological data, and qualitative interview data.

Results: The trials commenced recruitment in August 2019, and all data are expected to be collected by the end of May 2020. A user-centered design process is underway, with results from the first phase of user interviews indicating that people with mild cognitive impairment, family caregivers, and professional caregivers consider the SENSE-GARDEN to be a potentially valuable tool in providing numerous benefits to dementia care. Feasibility testing of the SENSE-GARDEN has been completed and results are expected to be published in October 2019.

Conclusions: Findings from the SENSE-GARDEN trials will provide insights into the use of technology for personalizing interventions to the PWD. This will have potential implications on not only dementia research, but it may also have influences on care practice.

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KEYWORDS

dementia; emotions; technology; multimedia; eHealth

Introduction

Background

Dementia is an umbrella term for a variety of neurodegenerative diseases that most often affect memory, behavior, and communicative abilities [1]. There are approximately 47 million people living with dementia worldwide [2]. With this number set to increase to 131.5 million by 2050, it is of the utmost importance to tackle dementia's progressive impact on the well-being of people living with a diagnosis. The World Health Organization (WHO) has called for action on dementia, presenting it as a public health priority at a global level [1]. This action includes a call for research to identify ways of supporting the needs of people living with dementia, their caregivers, and society in the context of costs, understanding, and awareness.

People with dementia (PWDs) progressively disconnect from the world; they experience loss of function, especially memory, affecting their cognition, physical activity, and verbal and nonverbal communication. A person's ability to communicate with others progressively worsens during the course of dementia, which can lead to the individual engaging in problem behaviors as an expression of unmet needs [3,4]. This can then result in an increase in caregiver burden for family members and residential care staff.

Continuing social contact with others and participating in activities is important for maintaining quality of life. Participating in past pleasant activities has an impact on functional ability and psychological well-being for PWDs living in residential care [5]. However, care facilities often struggle to fulfil this need for engagement and active participation, especially for residents in more advanced stages of cognitive and physical impairment [6]. This lack of external stimuli in the care environment can cause PWDs to become increasingly depressed [7].

In recent years, studies have identified numerous complex needs of PWDs living in long-term care. These include management of challenging behaviors, maintenance of social relationships, involvement of people with cognitive deficits in meaningful activities, and supporting the emotional needs of all [8,9]. Emotion-oriented approaches to care have been shown to be cost-effective ways of improving psychological well-being and social behavior among PWDs [10,11]. These nonpharmacological approaches are often person-centered, focusing on the personal, social, and emotional needs of the individual. Reminiscence rooms, virtual gardens, and virtual reality forests are examples of how immersive technologies have been integrated in emotion-oriented approaches designed to create effective interventions for PWDs [12,13]. However, this area of study has called for further research in determining what works best for the individual [6]. It has recently been suggested that an individualized multisensory environment for PWDs would be a highly beneficial intervention, especially if family members are included in the selection of stimuli [14]. Our research builds on this suggestion, creating not only a personalized multisensory intervention but one that also incorporates immersive technology, all with the inclusion of family members, friends, and professional care staff.

SENSE-GARDEN Intervention

The study is performed as part of the SENSE-GARDEN EU project, funded by the Active Assisted Living (AAL) Program Call 2016. It is a 3-year project that brings together a consortium of partners across Belgium, Norway, Portugal, and Romania. This multidisciplinary project is embracing a user-centered design approach throughout the development and implementation of the intervention. The SENSE-GARDEN intervention addresses the need for individualized approaches to dementia care by creating a multisensory environment that automatically adapts to the individual with dementia. Through integrating autobiographical music, films, images, and scent with technology, the SENSE-GARDEN is able to offer an immersive experience tailored specifically for the individual based on an individual profile including preferences in music, images, videos, and personal media, such as family photos.

The project aims at creating virtual spaces that are automatically adaptable to the personal memories and individual preferences of the users. The design of the space is shown in Figure 1. These spaces will be designed to strengthen the awareness of older PWDs by combining multisensory stimulation with physical activity and techniques from reminiscence therapy and Montessori methods. This stimulation of sight, touch, hearing, balance, and smell is expected to lead to a reconnection with reality for the PWD, resulting in an improvement in overall well-being and quality of life. The intervention will use a combination of various activities and approaches:

- *Reality Wall:* This is the projection of landscape videos, with some including familiar scenery and known places, onto a large wall.
- *Move to Improve:* This is an augmented reality game aimed at improving balance and increasing levels of physical activity.
- *Memory Lane:* This is an interactive touchscreen device showing family photographs and media from the individual's life story.
- *Life Road:* This is a stationary bicycle placed in front of a film showing a familiar place to the PWD.
- *Sounds Surround Me:* These are sounds from the surrounding sound speakers playing familiar music and background soundscapes.
- *Scents to Memories:* This is an olfactory dispensary system releasing familiar scents.
- *Films of My Life:* This is a collection of classic film excerpts meaningful for the PWD, together with family movies.

The rationale to include these elements in the SENSE-GARDEN intervention stems from the current evidence base of ways to

improve the well-being of PWDs. For instance, there has been an increasing amount of research on combining biographical information with multimedia apps to create digital *life stories*. Research on multimedia biography apps for PWDs has shown numerous benefits, such as stimulating reminiscence, evoking positive emotions, stimulating social interaction with others, and improving autobiographical memory [15-17].

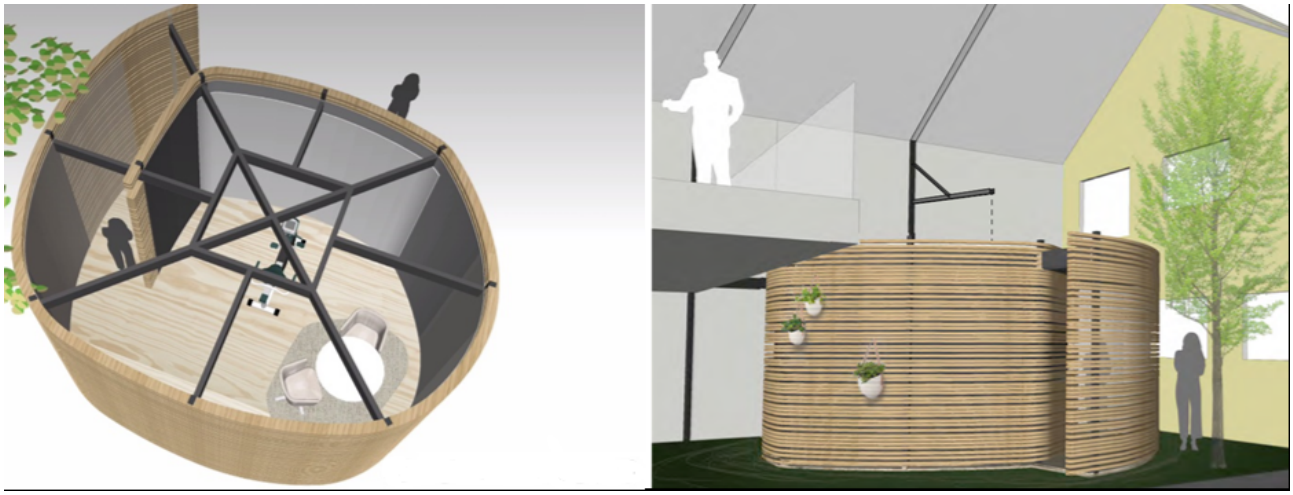
Research also suggests that there is potential to use technology to create immersive environments in dementia care. A recent study investigated the effects of a *virtual reality forest* on PWDs, in which large screen projection of scenery such as a forest or river was used in combination with movement sensors to create an immersive and interactive environment [13]. Although this environment was not based on the biographical information of the user, results showed improved levels of pleasure and alertness during the intervention.

Considering the promising results of these studies, the innovative approach of SENSE-GARDEN has the potential to provide numerous benefits to its users. Together, it was anticipated that the integration of these components and various stimuli would complement each other to create an immersive environment that the PWD can connect with, for example, pictures of forest scenery could be combined with the sound of singing birds and the odor of a pine forest. Other scenarios may include seas, streets, the beach, urban, or rural areas according to the most meaningful memories of each individual PWD. Having this immersive environment tailored to the individual memories of each user will create a connection to the more active areas of the memory; such stimuli may result in various types of emotional states.

Another important aspect of SENSE-GARDEN is the aim to support PWDs in sharing their life story with a caregiver. The theoretical underpinnings of this aim can be linked to previous study conducted on dementia and narrative. The literature has commented on the important role of digital media in conveying narratives and supporting meaningful conversations for PWDs and their caregivers [18]. By interacting with the various stimuli together with a caregiver, it is hoped that the PWD is able to reminisce on their past and become engaged in the *present moment*. The SENSE-GARDEN encourages PWDs to exercise at both mental and physical levels and takes them back into places they feel connected to. They can, for example, cycle or walk in a well-known space and feel like they are going home. Such experiences may have an effect on invigorating their identity and helping to recover their sense of self.

Relatives will have a key role in the initial adaptation of the space by providing information regarding the past of the user. After this initial setting, the SENSE-GARDEN will automatically adjust to the individual person. Feedback during the sessions will allow the SENSE-GARDEN system to learn the preferences of each user, meaning that the sessions will become increasingly personalized with each visit.

Figure 1. Architectural sketches of the SENSE-GARDEN space (left:interior, right: exterior).



Objectives

The study will test operational SENSE-GARDENs installed in the 3 study sites: Belgium, Norway, and Portugal. With these countries, a large coverage of the European context is achieved, allowing to study cultural, social, economic, and legal differences between the countries and European regions. The primary objective of this study is to determine whether the delivery of the innovative technology developed in SENSE-GARDEN can improve well-being in older adults with intermediate to advanced dementia. The WHO defines health as the “state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” [19]. This study will adopt this holistic approach to health and well-being by measuring well-being through primary outcomes related to behavior, activities of daily living, cognitive function, quality of life, self-identity, communication, and social presence.

Primary Outcomes

The study will examine 2 quantitative and 2 qualitative primary outcomes for the PWD, namely, reduction in behavioral and psychological symptoms in dementia (BPSD), improvement in cognitive function, increase in the feeling of social presence, and an increase in self-awareness and engagement. The primary outcomes for the informal caregiver (family caregivers) are a reduction in carer burden, improvement in carer coping and relief from stress, an increased quality of visits from the informal caregivers to the PWD, and an improvement in the quality of the relationship with their relative with dementia. The primary

outcome for the professional caregiver is a reduction in caregiver burnout.

Secondary Outcomes

Secondary outcomes for the PWD are changes in the prescription of medication, International Classification of Functioning, Disability, and Health (ICF) scores, mortality rate compared with previous existing records, number of hospitalizations comparing control and intervention groups, and an improvement in physical function and balance.

Exploratory Outcomes

Some interesting outcomes will be measured with an exploratory aim, but because of their nature as explained ahead, they may not allow for clear conclusions to be drawn. Instead, the purpose of these outcomes is to provide preliminary insights that can be built upon in future studies. These outcomes are as follows: a reduction in depressive symptoms and loneliness, relief from feelings related to the care burden, and improvement in quality of life.

The outcomes regarding depression and relief from feelings related to care burden are measured by means of semistructured interviews. The inclusion of people in later stages of dementia means that there may be challenges in applying these measures to all participants in the study.

A total of 4 months is a short amount of time, and therefore, it is not expected that a large improvement in the quality of life will be observed during this period. However, a small change in the quality of life may provide rationale for future longitudinal studies of the use of SENSE-GARDEN in dementia care, in which quality of life can be examined to a greater extent.

Physiological data will also be collected during the SENSE-GARDEN sessions. The Empatica E4 [20] will be used to collect information on electrodermal activity (EDA) and heart rate. These will be assessed during SENSE-GARDEN visits, as reaction to different stimuli. Data will be collected from a subgroup of participants, depending on their tolerance to use a wristband-mounted device. The device is validated for clinical use. Previous research on nonpharmacological interventions has used the E4 wristband to measure engagement and arousal states in people with mild to moderate dementia [21].

Methods

User-Centered Design

To ensure that the SENSE-GARDEN meets the needs of the users, the project has adopted a user-centered design approach to the development of the intervention. This user-centered design process is divided into 3 phases. An overview of the phases is shown in Figure 2.

The first phase focuses on collecting an initial impression of the user experience with nonfunctional low-fidelity prototypes of the SENSE-GARDEN (eg, mock-ups). Small groups of users will be invited to each test site to give their feedback on the overall concept of SENSE-GARDEN. These user groups will include professional care staff, family caregivers, and people living with mild cognitive impairment. Including these individuals at an early stage of the project will ensure that their views are incorporated into the development of SENSE-GARDEN.

The second phase focuses on creating experiences for individual users and aims at gaining a deeper understanding of the users' needs and requirements. An Alpha version of the SENSE-GARDEN system will be available for this phase of testing. This initial prototype of the SENSE-GARDEN will be tested in a controlled environment. Following the test, a semistructured interview will be conducted with the user to gain a rich insight into their experience.

The third phase involves feasibility testing of the system in the form of pretrials. A small number of users will be recruited at each site (1-2 users). The SENSE-GARDEN test will be tailored to each individual user by using personalized media content, such as family photographs, videos from holidays, and favorite music. The purpose of these tests is to not only ensure that the system works but also define the process of creating individualized experiences for each user.

Study Design

For the full trials, a controlled before-after study design will be used. The timeline for the study is shown in Figure 3. All participants eligible for the study will receive the SENSE-GARDEN intervention for 3 months. For the final month of the study, half of the participants (the intervention group) will continue to receive the SENSE-GARDEN intervention. The other half of the participants (the control group) will discontinue visits to the SENSE-GARDEN, receiving only normal care. The randomization procedure will use sealed envelopes and will be performed by the local researcher at each test site. The total number of envelopes will be prepared before the recruitment period. A sealed envelope will be assigned to each participant at the time of her or his enrolment. This randomization is to determine whether visits to the SENSE-GARDEN have lasting effects.

The study will start in August 2019, with a recruiting period of 6 months. The intervention period for each participant will be 3 months, followed by 1 month in either the intervention or control condition. The total study period will be 10 months.

Figure 2. Overview of user centred design process.

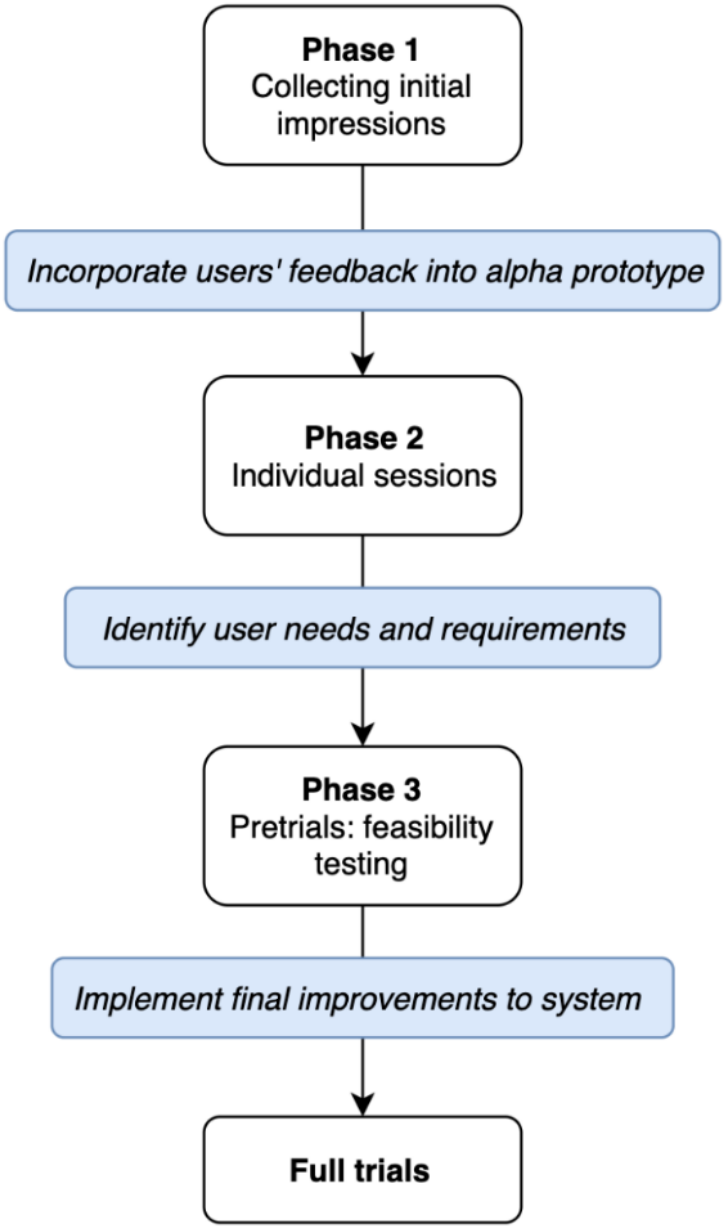
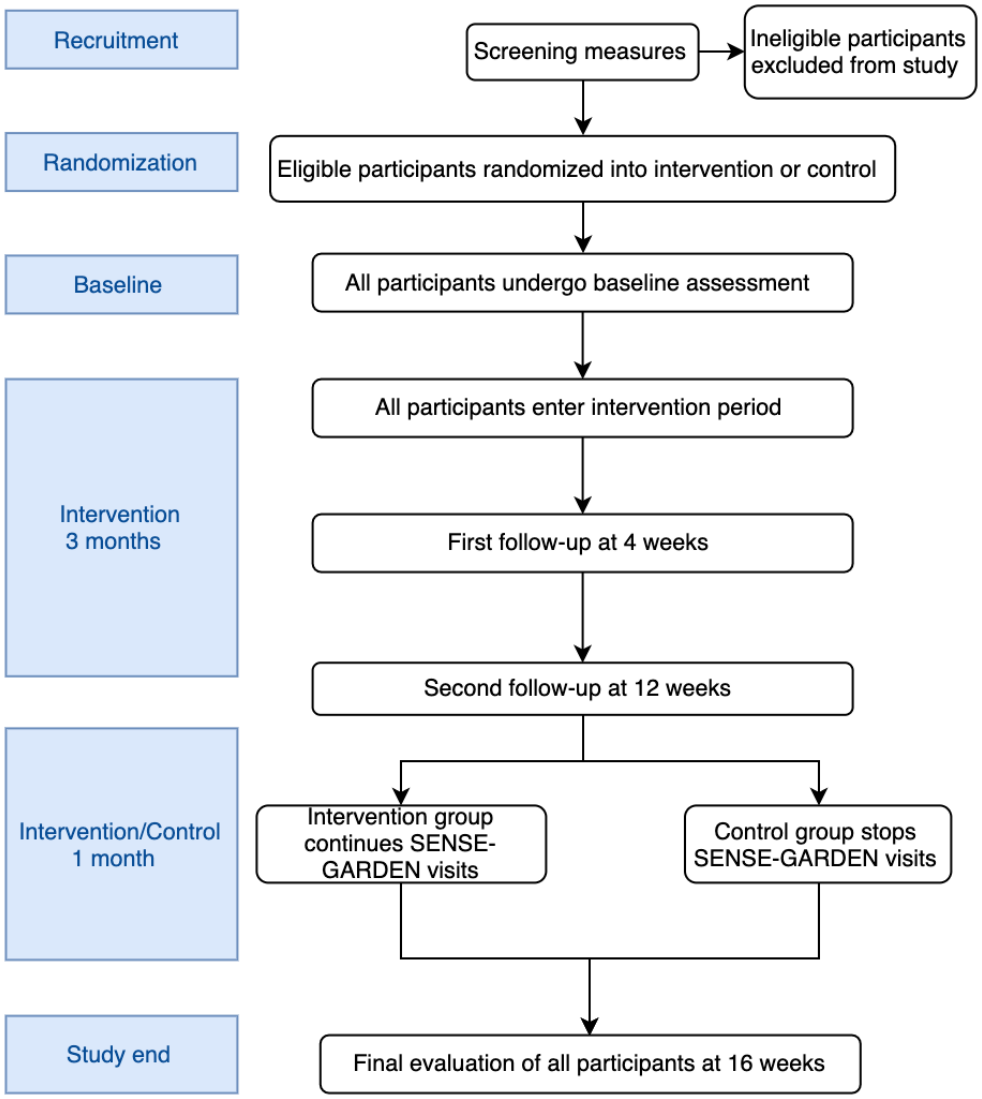


Figure 3. Study timeline.



Description of Test Sites

There will be 3 sites in 3 trial countries: Belgium, Norway, and Portugal. With these countries, a large coverage of the European context is achieved, allowing to study cultural, social, economic, and legal differences between the countries and European regions.

The test site in Belgium will be Aan de Beverdijk care home based in Hamont-Achel. This care home is part of the VULPIA group, a care provider that comprises 22 elderly care homes. Aan de Beverdijk focuses on providing tailored care based on the individual needs of its 90 residents. The test site in Norway will be Odda sjukeheim, a municipality-based care home for the elderly based in the center of Hardanger. The test site in Portugal will be the Lar Santa Joana Princesa care home for the elderly. This care home is a part of the Santa Casa de Misericórdia de Lisboa (SCML). SCML operates according to a humanitarian goal, and its care homes focus on promoting the quality of life of its residents.

Although it is inevitable that there will be differences among care homes, the SENSE-GARDEN space at each site is being custom-built for the specific purposes of this project. Each SENSE-GARDEN will have the same equipment, the same software and will be in a closed, private room. Having a controlled space at each test site will help reduce the amount of variability among the 3 countries.

Participants

This study will recruit a total of 55 PWDs living in care facilities, in a multisite trial with 3 sites. Details for each site are as follows: (1) Belgium—1 study site, 25 PWDs, 25 informal caregivers, and 3 professional caregivers, (2) Norway—1 study site, 15 PWDs, 15 informal caregivers, and 3 professional caregivers, and (3) Portugal—1 study site, 15 PWDs, 15 informal caregivers, and 3 professional caregivers.

Recruitment

Participants will be recruited at each study site by a professional caregiver from the SENSE-GARDEN team. The caregivers will inform potential participants about the study with the use of an information leaflet about the project. The potential participants who are interested in the study can then voluntarily express their willingness to participate. The participants who do not express an interest will not be contacted by the project team.

Professional caregivers included in the study will have at least 6 months experience in caring for dementia patients and a background in either nursing, occupational therapy, or physiotherapy or another relevant background when supported by long-term professional experience as a caregiver.

Before the study, the professional caregiver will have a 1-week training in SENSE-GARDEN use. This training comprises guidance on how to collect information from the participant and/or their family members for creating a user profile, upload media contents to the SENSE-GARDEN system, create *workflows* of media contents for individual SENSE-GARDEN sessions, and control the numerous elements in the SENSE-GARDEN space.

Each potential participant will undergo an assessment by a health professional for the evaluation of inclusion and exclusion criteria. For the participants fulfilling the criteria, a randomization to the intervention or control group will be performed.

Inclusion Criteria

To be included in the study, the participant must be aged ≥55 years and living with dementia in stage 2 (moderate) or stage 3 (severe) according to the Clinical Dementia Rating (CDR) Scale [22], possibly with comorbidities. The participant must also provide informed consent to participate (self-given or given by nominated legal tutor).

Exclusion Criteria

Other severe psychiatric disturbance diagnosed by Diagnostic and Statistical Manual of Mental Disorders (4th Edition, Text Revision) criteria, concurrent severe medical condition (extreme or disabling comorbidities), or physical disability not allowing participation in the SENSE-GARDEN activities.

Informal Caregivers

The informal caregiver should be a family member or close friend of the PWD. There will be at least 1 informal caregiver for each PWD recruited.

Inclusion Criteria

There is no age limit for the informal caregivers; they should have a computer and internet connection and provide signed informed consent to participate.

Study Procedures

During the 3 months of the intervention period, the PWD will visit the SENSE-GARDEN on an average of 3 times per week. Each participant should visit the SENSE-GARDEN a minimum of 25 times during the intervention period. Any participant who visits less than 25 times will be considered a dropout. On each visit to the SENSE-GARDEN, the PWD is accompanied by 1 caregiver (formal or informal). It is desirable that approximately one-third of the visits are performed with an informal caregiver.

Logs of interaction with the system will be collected continuously, including visit time and duration and system feedback given by the caregivers (through a tablet interface).

Observations will be made at 3 of the SENSE-GARDEN sessions during the intervention period. During this time, measurements on social presence and physical activity will be collected. Video recording will be required during the 3 observation sessions. The recordings will solely be used for data analysis and will not be shared. They will be accessible only to authorized researchers in charge of data analysis. Video recordings will only be made during sessions involving participants that have given their informed consent to being recorded.

For the control period, visits from the family will be logged during normal care.

Assessment Methods

The methods include the following types of data collection: self-reported measures, questionnaires, interviews, and observations. For interviews and questionnaires requiring the participation of the PWD, the capacity of the PWD to provide information will be considered. In the case of participants that are not competent to provide input, the tests will be performed with a proxy who will provide information on the patient's behalf. In some cases, the presence of both the PWD and proxy will be considered.

Screening Measures

The CDR Scale [22] will be used to assess the severity and progression of the individual's dementia. Only individuals at level 2 (moderate dementia) or level 3 (severe dementia) will be included in this study.

To decide how to best tailor the SENSE-GARDEN intervention to each individual participant, the Adolescent/Adult Sensory Profile will be used [23]. The Adolescent/Adult Sensory Profile is a tool that evaluates behavioral responses to sensory experiences, with categories focusing on taste and smell, touch, auditory processing, visual processing, movement, and activity level. This measure has recently been tested with people with severe dementia to identify individual sensory processing preferences [24]. This tool will be used in the SENSE-GARDEN study to determine the most appropriate level of sensory stimulation for each participant.

Outcome Measures

The following measures will be applied at baseline (T0), 4-week follow-up (T1), 12-week follow-up (T2), and a final follow-up at 16 weeks (T3). An overview of these measures is given in Table 1.

Table 1. Overview of outcome measures.

Outcome	Measurement	Timepoint
Outcome for the person with dementia		
A reduction in BPSD[a]	CMAI[b] and BANS-S[c]	T0[d], T1[e], T2[f], T3[g]
Improvement in quality of life	QUALID[h]	T0, T1, T2, T3
Reduction in depressive symptoms and loneliness	CSDD[i]	T0, T1, T2, T3
Increase in the feeling of social presence	OERS[j], OME[k], VNVIS-CR[l]	T1[m], T2[m], T3[m]
Improvement in cognitive function	Mini-Cog[n], FAST[o], GDS[p]	T0, T1, T2, T3
Relief from feelings related to the care burden	Semistructured interview	T3
Increase in self-awareness and engagement	Audio recordings analyzed using conversation analysis	T1[m], T2[m], T3[m]
ICF[q] scores	WHODAS 2.0[r]	T0, T1, T2, T3
Prescription of medication	Medical records	T0, T1, T2, T3
Mortality rate compared with previous existing records	Medical records	T0, T1, T2, T3
Number of hospitalizations comparing control and intervention groups	Medical records	T0, T1, T2, T3
Exploration of physiological data including electrodermal activity and heart rate	Empatica E4 wristband	T1[m], T2[m], T3[m]
Improvement in physical function and balance	FRT[s]	T0, T1, T2, T3
Outcome for the informal caregiver		
A reduction in caregiver burden	ZBI[t]	T0, T1, T2, T3
Improvement in caregiver coping and relief from stress	Brief-COPE[u]	T0, T1, T2, T3
An increased quality of visits to the person with dementia	FAVS-D[v]	T0, T1, T2, T3
An improvement in the quality of relationship with the person with dementia	QCPR[w]	T0, T1, T2, T3
Outcome for the formal caregiver		
Reduction in caregiver burnout	MBI-HSS[x]	T0, T1, T2, T3

[a]BPSD: behavioral and psychological symptoms of dementia.
[b]CMAI: Cohen–Mansfield Agitation Inventory.
[c]BANS-S: Bedford Alzheimer Nursing Scale–Severity.
[d]T0: baseline.
[e]T1: 4-week follow-up.
[f]T2: 12-week follow-up.
[g]T3: 16-week follow-up.
[h]QUALID: Quality of Life in Late Stage Dementia scale.
[i]CSDD: Cornell Scale for Depression in Dementia.
[j]OERS: Observed Emotion Rating Scale.
[k]OME: Observational Measurement of Engagement.
[l]VNVIS-CR: Verbal and Nonverbal Interaction Scale.
[m]Measurement to be taken during SENSE-GARDEN session.
[n]Mini-Cog: 3-min instrument to screen for cognitive impairment in older adults.
[o]FAST: Functional Assessment Staging Tool.
[p]GDS: Global Deterioration Scale.
[q]ICF: International Classification of Functioning, Disability and Health.
[r]WHODAS 2.0: World Health organization Disability Assessment Schedule 2.0.
[s]FRT: Functional Reach Test.
[t]ZBI: Zarit Burden Interview.
[u]Brief-COPE: abbreviated version of the Coping Orientation to Problems Experienced inventory, a self-report questionnaire.

[v]FAVS-D: Family Visit Scale for Dementia.

[w]QCPR: Quality of Carer Patient Relationship scale.

[x]MBI-HSS: Maslach Burnout Inventory–Human Services Survey.

Person With Dementia

Primary Outcomes

A Reduction in Behavioral and Psychological Symptoms in Dementia

The Bedford Alzheimer Nursing Scale–Severity (BANS-S) [25] and the Cohen–Mansfield Agitation Inventory (CMAI) [26] will be used to determine whether the intervention reduces behavioral and psychological symptoms of dementia. BANS-S is a nursing staff–administered questionnaire that assesses dressing, sleeping, speech, eating, mobility, muscles, and eye contacts in persons with severe dementia. It is a reliable measure with good internal consistency (Cronbach alpha=.64-.80). CMAI is a widely used tool that evaluates aggressive behavior, nonaggressive behavior, and verbally aggressive behavior. The caregiver-rated questionnaire comprises 29 agitated behaviors, each rated on a 7-point scale of frequency ranging from 1 (never) to 7 (several times an hour).

Increase in the Feeling of Social Presence

Observational measures will be used to determine the level of social engagement in the participants with dementia. These tools will be the Observed Emotion Rating Scale (OERS) [27], the Verbal and Nonverbal Interaction Scale (VNVIS-CR) [28], and the Observational Measurement of Engagement (OME) [29]. All 3 measures have previously been used in studies observing people living with dementia. OERS assesses pleasure, general alertness, anxiety or fear, and sadness at 10-min intervals. VNVIS-CR is a tool developed specifically to measure verbal and nonverbal interaction in people with mild to moderate dementia. The 26 items assess nonverbal social behaviors, nonverbal unsociable behaviors, verbal sociable behaviors, and verbal nonsociable behaviors. The OME evaluates various dimensions of engagement in people with mild to severe dementia. The tool measures attention to stimulus, attitude toward stimulus, rate of refusal, duration, and activity.

Observations will be made during at least 2 of the SENSE-GARDEN sessions for each participant. For participants in the intervention group, recordings will be taken during a SENSE-GARDEN session in week 4, week 12, and week 16. Participants randomized to the control group will only have recordings taken during a session in week 4 and week 12, as these individuals will no longer be visiting the SENSE-GARDEN after week 12.

Improvement in Cognitive Function

The Mini-Cog [30], the Functional Assessment Staging Tool (FAST) [31], and the Global Deterioration Scale (GDS) [32] will be used to assess whether there is any improvement in cognitive function among the participants. The Mini-Cog is an assessment of cognitive function that only takes 2 to 5 min to complete. It comprises a word recall task and a clock drawing test. FAST is a dementia staging tool that focuses on an individual's level of functioning and ability to carry out activities of daily living. Scores range from 0 to 7, with a higher score indicating an increased level of functional decline. GDS is a brief dementia staging scale that assesses the stage and progression of dementia in terms of cognitive decline. Scores range from 0 to 7, with a higher score indicating a more severe level of cognitive decline.

Increase in Self-Awareness and Engagement

Conversation analysis will be used to assess the PWD's level of self-awareness and engagement with both the SENSE-GARDEN stimuli and the caregiver conducting the session. To conduct conversation analysis, audio recordings of certain SENSE-GARDEN sessions will be taken.

Secondary Outcomes

Medical records will be used to assess prescription of medication and mortality rate compared with previous existing record, and they will also be used to compare the number of hospitalizations between the control and intervention groups.

ICF scores will be collected using the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) [33]. The WHODAS 2.0 is a tool for measuring functioning and disability in accordance with the ICF framework. The tool assesses 6 domains of functioning: cognition, mobility, self-care, getting along with others, life activities, and participation in community activities. This study will use the 36-item version that can either be self-administered or administered by a proxy or interviewer.

The Functional Reach Test (FRT) [34] will be used to assess any improvement in physical function and balance.

The FRT is a widely used tool to screen for balance problems in older adults. The test comprises a brief physical task that asks the individual to reach forward without moving his or her feet. The test measures the amount of maximum excursion that the individual is able to cover without losing balance or taking a step.

Exploratory Outcomes

Physiological Data

The Empatica E4 [20] will be used to measure physiological responses to the SENSE-GARDEN stimuli. These physiological responses will include heart rate and EDA.

A Reduction in Depressive Symptoms and Feelings of Loneliness

The Cornell Scale for Depression in Dementia (CSDD) [35] will be used to determine any reduction in depressive symptoms and feelings of loneliness in PWDs. The CSDD is a measure of depression among people with moderate to severe dementia, making it an appropriate choice for the SENSE-GARDEN study. The 19-item tool assesses mood-related signs of depression, behavioral disturbance, physical signs, cyclic functions, and ideational disturbance. It is administered in the form of a semistructured interview by a health care professional or clinician.

An Improvement in Quality of Life

The Quality of Life in Late Stage Dementia (QUALID) scale [36] is the only scale developed for advanced dementia and will, therefore, be used to determine any improvement in quality of life in this study. It was created to appreciate the outcome of clinical management, including the effect of therapeutic interventions. QUALID contains 11 items that describe observable behaviors, such as emotional state, interaction with others, aggression, and physical signs of discomfort. It is completed by a health care professional or a family caregiver.

Relief From Feelings Related to the Care Burden

A semistructured dyadic interview will be conducted with the PWD and their family caregiver at the end of the study period. This interview will be used to explore the relationship between the 2 individuals. One factor will be the relief from feelings related to the care burden.

Informal (Family) Caregiver

A Reduction in Caregiver Burden

The Zarit Burden Interview [37] will be used to measure caregiver burden. The tool is a self-report measure that evaluates a caregiver's health, psychological well-being, finances, social life, and relationship shared with the PWD. Scores range from 0 to 88, with a higher score indicating a higher level of burden.

An Improvement in Caregiver Coping and Relief From Stress

The Brief-COPE [38] is a shortened version of the Coping Orientation to Problems Experienced (COPE) inventory [39] and will be used to determine any improvement in the coping strategies in family caregivers. The Brief-COPE is a self-reported measure comprising 28 items that assess the following coping strategies in caregivers: emotion-focused strategies, problem-focused strategies, and dysfunctional coping strategies.

An Increased Quality of Visits to the Person With Dementia

The Family Visit Scale for Dementia [40] will be used to evaluate the quality of visits from the family members to the participants with dementia. The questionnaire is completed by the family member and evaluates nursing staff interaction with residents and visitors, meaningfulness of the visit, cleanliness, and connection established between the visitor and the resident.

An Improvement in the Quality of the Relationship With the Person With Dementia

The Quality of Carer Patient Relationship scale [41] will be used to assess an improvement in the relationship between the PWD and the family caregiver. This scale comprises 14 items that assess the level of warmth in the relationship and the absence of criticism.

Formal (Professional) Caregiver

A Reduction in Caregiver Burnout

The Maslach Burnout Inventory–Human Services Survey (MBI-HSS) [42] will be used to assess caregiver burnout in professional caregivers. The MBI-HSS is an extensively used tool for measuring burnout in professionals working in human services. The tool focuses on emotional exhaustion, depersonalization, and personal accomplishment.

Data Analysis

Quantitative data will be analyzed using SPSS Statistics version 25 (IMB Corp). Stratification by gender, age, and type and stage of dementia will be used to analyze the data. Repeated measures analysis of variance (ANOVA) will be used to assess whether the SENSE-GARDEN intervention has an effect on participants over time. Given the novelty of the SENSE-GARDEN intervention, it is not possible to assess the previous literature for clinically meaningful differences. However, Cohen *d* has been used to determine effect size in studies focusing on the effects of nonpharmacological interventions on behavioral outcomes in PWDs [43].

Cohen *d* is a measure of standardized difference between 2 means [44]. It uses standard deviation units to express the magnitude of difference between the 2 means, indicating the importance of the difference. Cohen has defined a small effect size as d=0.2, a medium effect size as d=0.5, and a large effect size as d=0.8.

For this study, repeated measures ANOVA will be performed on the data using SPSS to assess the effects of the intervention over the numerous time points (T0-T3). We estimate that a sample size of 55 will have over 80% power to detect a medium difference between means at a .05 significance level.

Qualitative interview data will be analyzed using thematic analysis [45]. Thematic analysis is a method of identifying patterns of prevalent ideas or responses and can offer rich insight into the attitudes and beliefs of participants. This aspect of the study will be vital for understanding the users' experiences of the SENSE-GARDEN.

Ethical Approval and Considerations

Applications for ethical approval have been submitted by the 3 study sites in accordance to the national regulation. This study has been submitted to Norway's Regional Committee for Medical and Health Research Ethics and is currently under assessment (document ID 1094463).

Confidentiality and Privacy

Confidentiality of private health information will be ensured according to the regulation (EU) 2016/679 (General Data Protection Regulation). All private personal data will be deidentified: every unique identifying number, characteristic, or code identifier of the individual, relatives, or employers will be removed, so that the information can be used alone or in combination with other information. The resulting data will be analyzed by a statistician to ensure that no individually identifiable health information remains.

Informed Consent

The consent of participants will be required. They will be provided a letter of informed consent to be signed, together with an information sheet. The participants will be informed regarding the study's aims and protocol and what involvement the study will comprise. The participants will be made aware of their right to withdraw from the study at any time.

Information regarding confidentiality and data protection will be given. The letter of consent will be signed by the patient, when competent, or otherwise a legal tutor, signing as proxy.

Exit Strategy

An important ethical consideration for users is the exit strategy at the end of the project. All care organizations in the consortium have initially expressed their interest in evaluating the potential of keeping the SENSE-GARDEN after project end. The YOUSE GmbH method will be used also in connection with the exit strategy.

Results

The trials commenced recruitment in August 2019. All data are expected to be collected by the end of May 2020. All phases of the user-centered design process have taken place, which has helped shape the development of SENSE-GARDEN. The results of the first phase have been published and presented at the Fourth International Conference on Human and Social Analytics 2018 (in press). Interviews with 52 users comprising people with mild cognitive impairment and informal and formal caregivers were conducted in November 2017. The aims of these interviews were to collect initial responses and attitudes toward the SENSE-GARDEN concept and investigate what benefits, if any, the users thought SENSE-GARDEN could provide in the care of PWDs.

The interviews were analyzed using thematic analysis [45]. A total of 6 themes were identified: benefits for all, shared experiences, past and present, focus on the individual, emotional stimulation, and challenges to consider. The ideas expressed by the users provided rich insights into how the SENSE-GARDEN intervention should be implemented. For example, a point raised by the users was the importance of caregiver facilitation. Although it is important for the SENSE-GARDEN system to work correctly, it will be essential to involve a caregiver who is able to facilitate the session in a safe and effective way. From this feedback, we are working on creating user training materials that will help the caregivers use the system and also aid them in creating meaningful experiences for the PWD.

Results from the second phase of the user-centered design process emphasized the importance of including personalized media contents. At the Norwegian test site, 3 user tests were conducted in a room with a prototype of the SENSE-GARDEN. The first test involved an 85-year-old lady with early-stage dementia and a professional caregiver. This lady did not feel *connected* to the media and also felt that the session was too fast. The second test involved an 89-year-old lady with early-stage dementia and a family caregiver. This session was extremely positive, with the user expressing positive emotions toward the films played during the session. The user was only able to remember watching 1 of the videos played during the session (a video of Norwegian folk dancing); however, she spoke about this video fondly during the semistructured interview after the session. Finally, the third test involved an older adult aged 85 years without cognitive impairment and 2 professional caregivers. This was again a very positive session, and the 3 individuals enjoyed talking together about the videos that they were watching. Testing at the other sites has also affirmed that users respond better to personalized or familiar media contents.

The third phase of user testing has been completed, which evaluated functional prototypes of the SENSE-GARDEN system. An example of a SENSE-GARDEN prototype is shown in Figure 4. Results from this feasibility testing are expected to be submitted for publishing in October 2019.

Figure 4. Photo of a test session using a prototype of SENSE-GARDEN.

Discussion

Summary

This paper has outlined the objectives, study design, and preliminary results of an AAL-funded study, SENSE-GARDEN. To our knowledge, SENSE-GARDEN is the first intervention to combine multisensory stimuli, virtual technology, and autobiographical material to create an immersive and personalized room for PWDs. Our progress thus far has indicated the value of involving user groups in the initial stages of intervention development and has shown that these users have a positive outlook toward SENSE-GARDEN. The evaluation summary report has been provided in Multimedia Appendix 1.

Limitations

A limitation of this study proposal is its small sample size. However, although the study may not be able to produce generalizable results, it will provide important insights into the use of a novel technology, such as SENSE-GARDEN for PWDs. The results will provide foundation for further study in the use of immersive, individualized environments and how these environments can be used to facilitate communication and person-centered care in residential care home environments.

A further limitation is the potential variance between the test sites. Implementing this study protocol in 3 different countries may be difficult in terms of ensuring that the SENSE-GARDEN intervention is delivered in the same manner in each care home. Cultural differences between the test sites may mean that methods of facilitation from care home staff could affect the overall SENSE-GARDEN experience, therefore, influencing the results from the study. However, all professional care staff will be given the same training on how to use the SENSE-GARDEN. This training should help to ensure that the intervention is conducted in a similar way at each test site.

Conclusions

Despite these limitations, this study has the potential to provide important contributions to current research on dementia care. The interdisciplinary nature of this project will allow us to evaluate the SENSE-GARDEN from multiple perspectives, such as technical, sociological, and psychological. The findings from the full trials have the potential to offer numerous implications on future research in dementia care and also in promoting person-centered care in practice.

Acknowledgments

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Authors' Contributions

This protocol is based on a funded grant proposal. All coauthors contributed to the design of the study and participated in the initial user-centered design phase of the project. IC, AM, RD, MZ and MB provided clinical expertise on the decision of outcome measures. GG and AS drafted the paper. IC, KT, JS, AM, RD, MZ, MB, and WM reviewed and helped produce the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Active Assisted Living evaluation summary report.
[PDF File (Adobe PDF File), 54 KB - resprot_v8i9e14096_app1.pdf]

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Abbreviations

AAL: Active Assisted Living
ANOVA: analysis of variance
BANS-S: Bedford Alzheimer Nursing Scale–Severity
BPSD: behavioral and psychological symptoms of dementia
CDR: Clinical Dementia Rating
CMAI: Cohen–Mansfield Agitation Inventory
CSDD: Cornell Scale for Depression in Dementia
EDA: electrodermal activity
FAST: Functional Assessment Staging Tool
FRT: Functional Reach Test
GDS: Global Deterioration Scale
ICF: International Classification of Functioning, Disability and Health
MBI-HSS: Maslach Burnout Inventory–Human Services Survey
OERS: Observed Emotion Rating Scale
OME: Observational Measurement of Engagement
PWDs: people with dementia
QUALID: Quality of Life in Late Stage Dementia scale
SCML: Santa Casa de Misericórdia de Lisboa
VNVIS-CR: Verbal and Nonverbal Interaction Scale
WHO: World Health Organization
WHODAS 2.0: WHO Disability Assessment Schedule 2.0

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Protocol

Health Disparities in Staphylococcus aureus Transmission and Carriage in a Border Region of the United States Based on Cultural Differences in Social Relationships: Protocol for a Survey Study

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Abstract

Background: Health care–associated *Staphylococcus aureus* infections are declining but remain common. Conversely, rates of community-associated infections have not decreased because of the inadequacy of public health mechanisms to control transmission in a community setting. Our long-term goal is to use risk-based information from empirical socio-cultural-biological evidence of carriage and transmission to inform intervention strategies that reduce *S aureus* transmission in the community. Broad differences in social interactions because of cultural affiliation, travel, and residency patterns may impact *S aureus* carriage and transmission, either as risk or as protective factors.

Objective: This study aims to (1) characterize *S aureus* carriage rates and compare circulating pathogen genotypes with those associated with disease isolated from local clinical specimens across resident groups and across Hispanic and non-Hispanic white ethnic groups and (2) evaluate social network relationships and social determinants of health-based risk factors for their impact on carriage and transmission of *S aureus*.

Methods: We combine sociocultural survey approaches to population health sampling with *S aureus* carriage and pathogen genomic analysis to infer transmission patterns. Whole genome sequences of *S aureus* from community and clinical sampling will be phylogenetically compared to determine if strains that cause disease (clinical samples) are representative of community genotypes. Phylogenetic comparisons of strains collected from participants within social groups can indicate possible transmission within the group. We can therefore combine transmission data with social determinants of health variables (socioeconomic status, health history, etc) and social network variables (both egocentric and relational) to determine the extent to which social relationships are associated with *S aureus* transmission.

Results: We conducted a first year pilot test and feasibility test of survey and biological data collection and analytic procedures based on the original funded design for this project (#NIH U54MD012388). That design resulted in survey data collection from 336 groups and 1337 individuals. The protocol, described below, is a revision based on data assessment, new findings for statistical power analyses, and refined data monitoring procedures.

Conclusions: This study is designed to evaluate ethnic-specific prevalence of *S aureus* carriage in a US border community. The study will also examine the extent to which kin and nonkin social relationships are concordant with carriage prevalence in social groups. Genetic analysis of *S aureus* strains will further distinguish putative transmission pathways across social relationship contexts and inform our understanding of the correspondence of *S aureus* reservoirs across clinical and community settings. Basic community-engaged nonprobabilistic sampling procedures provide a rigorous framework for completion of this 5-year study of the social and cultural parameters of *S aureus* carriage and transmission.

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KEYWORDS

S aureus carriage; S aureus transmission; community acquired S aureus transmission; social determinants of health; social network analysis; border health; health disparities in minority communities

Introduction

Overview

Staphylococcus aureus is a Gram-positive bacterium that lives in close association with humans as both a commensal and pathogen [1]. Methicillin-resistant *S aureus* (MRSA) and methicillin-sensitive *S aureus* (MSSA) infections have historically been considered a health care–acquired (HA) phenomenon. However, community-acquired (CA) MRSA and MSSA now represent the most common cause of skin and soft tissue infections (SSTIs) presenting to US emergency departments [2]. In 2017, an estimated 120,000 invasive MRSA infections occurred in the United States, with 20,000 associated deaths [3], whereas MSSA infections sometimes outnumber MRSA infections 3 to 1 [4]. Invasive MRSA infections in health care settings have been declining, but community MSSA infections are increasing slightly [3,5].

A number of significant challenges exist for controlling *S aureus* transmission in general populations. Even though rates of HA MRSA infections have declined since 2005 and 2007, they remain unacceptably high, and rates of CA MRSA have not decreased over this period [3,5-12]. About one-third of the healthy US population is thought to be asymptomatic carriers of *S aureus* with 1.5% being carriers of MRSA [13]. These carriers form an important community-based reservoir for MSSA and MRSA infections. Colonization and infection rates have not been thoroughly studied for Hispanics; however, there is evidence that MRSA colonization is lower for Hispanics than for non-Hispanic whites [14]. Although Hispanics have a lower risk of SSTIs than non-Hispanic whites [15], isolates recovered from SSTIs are more likely to be MRSA [15], which are associated with increased risk of MRSA infection [16]. However, local conditions impacting community health may modify these associations.

Transmission of *S aureus* occurs through contact with colonized individuals, animals, and contaminated surfaces. About a third of all Americans are thought to be asymptomatic carriers of *S aureus*, and about 1.5% of the general US population are carriers for MRSA [13]. Although the throat and nares are most often colonized, other warm and moist body sites such as the axillae, anus, vagina, and perineum are also frequently colonized [17-20]. *S aureus* can survive in the environment, depending on conditions, for over 90 days [21]. Importantly, hands can also be transiently colonized and can transfer the bacteria to other body areas and other individuals [4]. Persons colonized with *S aureus* are at risk of infecting themselves, although most do not develop clinical disease [4]. In a hospital setting, approximately 30% of MRSA colonized patients developed subsequent SSTIs [22].

Intervention programs have reduced MRSA in health care institutions, but a more thorough understanding of transmission networks is required for efficient and targeted mitigation of MRSA and MSSA in community settings. Comprehensive efforts to decolonize people and decontaminate their environment reduced but did not eliminate long-term carriage and recurrence of disease. For example, 49% of children infected with CA-*S aureus* were reinfected within 6 months of decolonization [23]. How are these patients becoming recolonized and reinfected? Unlike the more controlled hospital environment, transmission chains for CA-MRSA and MSSA are more complex, and sources may be more difficult to identify. On a limited basis, search and destroy principles have been extended into patient households and have involved decontaminating household surfaces and screening/treating family members and even pets [17,24]. In 1 study, after index patients were decolonized, 72% were reinfected after 12 months, and even when all household members were additionally decolonized, 52% of index cases were reinfected [25]. Importantly, social contacts within and outside the immediate household are likely to play a role in the transmission of [26].

The Yuma County Public Health District has identified *S aureus* (MRSA and MSSA) as a top public health priority in this border health district, based on community engaged environmental scans conducted by Northern Arizona University's (NAU's) Center for Health Equity Research in collaboration with the NAU-Yuma branch campus [27].

Study site is Yuma County, Arizona. It has an overall population of 212,128 (2018 estimate). The race and ethnicity breakdown of the resident population is 63.9% Hispanic, 30.8% white non-Hispanic, 2.7% African American, and 2.3% Native

American [28]. The majority of the population of Yuma County is concentrated in the southwestern corner near the city of Yuma (about 50% of the county's population). The US Department of Labor's Bureau of Labor Statistics ranked the unemployment rate of 389 metropolitan areas and found that Yuma has the third highest unemployment rate in the country, at 12.3% [29]. Yuma is identified as a medically underserved community. Nearby cities in the Imperial Valley of California (Calexico, El Centro, and Imperial) have a combined population of approximately 102,000 of which more than 86% are Hispanic. This entire region serves as the catchment area of the Yuma Regional Medical Center (YRMC). Yuma sustains a large agricultural labor force and frequent cross-border interactions with migrant farm worker populations from Mexico. In addition, an estimated 90,000 "winter visitors/residents" live in the area during the winter and early spring months. As a consequence of its large cross-border agricultural worker population, the ethnic make-up of the residential community, and seasonal population dynamics, the area surrounding Yuma, Arizona, provides a unique setting to investigate the social and biological parameters of *S aureus* carriage and transmission.

Research Questions

We are comparing community and clinical samples to examine ethnic-based carriage disparities. We will also determine whether *S aureus* transmission is associated with social network attributes and culturally based relations within each naturally occurring social group in the sample. The ability to compare MSSA and MRSA carriage and transmission within and between these groups presents a significant opportunity to examine the complexity of any carriage or infection-related health disparity. It also has the potential to establish improved models for intervention in culturally complex populations. Our research methods combine sociocultural survey data collection with population health, biological sampling, and genomic analysis. We will use a synthesis of approaches (asking participants questions designed to quantify contact within their naturally occurring social group and comparing the evolutionary relatedness of *S aureus* positive samples to infer transmission) to determine the extent to which social relationship characteristics are associated with *S aureus* transmission.

Specific aim 1 is as follows: We will determine if there is an ethnic and residency-based *S aureus* carriage disparity in Yuma, Arizona. We will also compare circulating pathogen genotypes isolated from asymptomatic community members with those associated with disease isolated from local clinical specimens.

Hypotheses are as follows: (1a) Ethnic-based disparities in *S aureus* infections extend to carriage in the populations of 2 ethnic groups (Hispanic and non-Hispanic white) in Yuma, Arizona. We will also test the null hypothesis (1b) that circulating *S aureus* genotypes do not differ among the ethnic groups and thus do not account for any observed disparities. To do this, we will obtain a community sample of *S aureus* by collecting samples from people recruited at multiple community sites and events. The genome sequences from this community sample will be compared with sequences from clinical *S aureus* samples collected from patients at local health care providers. Variables are as follows: We will collect nasal, oropharyngeal, and hand swabs to test for the presence of *S aureus* and thus determine the community carriage proportions across ethnicities and by part-time versus full-time resident groups. We will compare the proportions of community *S aureus* carriage to determine if these stratifications present a disparity. Positive samples will be sequenced and phylogenetically compared with genomes from clinical infection isolates collected at the YRMC. This will determine concordance, if any, between clinical pathogen genotypes and strains carried within the general population. In addition, we will determine if clinical and community strains are clustered by ethnicity and thus could partially explain discrepant likelihoods of *S aureus* infections.

Specific aim 2 is as follows: We will evaluate social network relationships and social determinants of health-based risk factors for their impact on carriage and transmission of *S aureus*.

Our hypothesis is as follows: (2a) Differences in the types and intensity of social contact behavior within and between the populations will result in differential *S aureus* transmission within social groups. While enrolling participants, we will target a variety of naturally occurring social groups (family, friends, and coworkers). We will determine the extent to which social relationships result in *S aureus* transmission by (1) asking participants questions designed to quantify direct and indirect physical contact within a group and (2) assessing the evolutionary relationships (transmission) among positive *S aureus* samples through phylogenetic analysis of whole genome sequences to confirm or refute putative transmission.

Methods

Baseline/Pilot and Feasibility Studies

The original community sampling design for the project was to collect both social and biological data over a 4-month window each year by interviewing individuals in naturally occurring groups and collecting biological specimens from those individuals, comprising 367 social groups (family/friendship clusters) in residential and public settings around Yuma, Arizona (Yuma Somerton, San Luis, and Rio Colorado), and nearby communities in the southernmost parts of the Imperial valley, California (Calexico, El Centro, and Imperial). Individuals were consented and enrolled into the study for biological sampling and assessment of social relationships. *S aureus* samples from the nose, throat, and hand of each participant were collected and are being processed for whole genome sequencing. The proportion of positive samples from individuals of each ethnicity are being compared with the proportional composition of each ethnicity in the naturally occurring social groups sampled. All *S aureus* isolates are undergoing whole genome sequencing and phylogenomic analysis to identify clustering by ethnicity, residential status, or geography. Clinical samples (residual diagnostic specimens) are being collected throughout the year to determine temporal patterns and determine if clinical isolates are representative of the genomic diversity present in the community samples. Data from the deidentified clinical samples include diabetes (yes/no), age, gender, ethnicity, and state of residency. We are using social determinants of health (education and wealth), individual-level social integration, and group-level

social network variables (both egocentric and relational) to determine the extent to which social relationships can explain or contribute to *S aureus* transmission. Social relationships and contact are being determined by asking participants questions designed to quantify physical contact within a social group. By comparing the evolutionary relatedness of *S aureus* genomes with the measured or estimated level of contact among participants, we will be able to determine social contact variables most likely linked to transmission.

Sampling Approach

In the year 1 baseline and feasibility study, we used a stratified purposive sampling approach [30-33] to capture naturally occurring social groups at both private and public venues in our study area. Recruitment consisted of inviting group members to participate in this study, assuming that their interactions represent a variety of direct and indirect contact relationships (close family and friends will interact more and be more likely to transmit *S aureus* compared with distant family members or acquaintances). Participant inclusion criteria was full-time or part-time residence in Yuma for at least 1 member of the social group. All members of the recruited social group were invited to participate in the project. Analysis of carriage by ethnicity will incorporate group clustering.

Given the potential sensitivity of human genetics research, informed consent is designed to clearly convey that no human genetic material will be maintained or analyzed. Each consented individual (or in the case of children; child assent and parental consent) was asked to complete the survey containing social and demographic information and to be swabbed (anterior nares, throat, and dominant hand) to detect both *S aureus* colonization. The genomes of *S aureus* cultures are being sequenced to determine strains and phylogenetic relationships to infer transmission within naturally occurring social groups. In addition, these genomes can be compared with *S aureus* genomes from clinical isolates collected across the same time period from the YRMC. As the primary catchment area of YRMC includes communities in Arizona and California that are targeted in this study, comparison of clinical and community genomes will allow us to determine if clinical isolates are representative of community isolates and if prevalent clinical isolates change over time.

Comparisons of carriage across ethnic lines will enable us to determine if there is a *S aureus* carriage disparity in the general population. Subsequent whole genome sequencing and phylogenetic analysis will allow us to determine if clinical *S aureus* strains are representative of the diversity of community strains and not because of the emergence of a few highly fit lineages. Phylogenetic analyses will also be used to exclude the possibility that *S aureus* populations differ along ethnic and residential groups, thus eliminating pathogen genotype as a partial explanation for any carriage or infection disparity. In addition, phylogenetic analyses will be used to identify possible transmission events within a social group. From all community participants, we have collected demographic, economic, and social interaction data. These data permit evaluation of the relative importance of social and demographic colonization and transmission determinants in this diverse border community. Using binary *S aureus* carriage (yes/no) as the outcome, we will use logistic regression to determine the strongest indicators of colonization and transmission in the community.

We are also evaluating social network– and social determinants–based risk factors for transmission of *S aureus*. While enrolling participants, we targeted a variety of social groups (family, friends, and coworkers). Whole genome sequencing and phylogenetic analyses of resulting *S aureus* genomes will allow us to determine if transmission has occurred between members of a social group. By asking participants questions designed to quantify direct and indirect physical contact with each member of the social group, we will be able to determine the extent to which social relationships are associated with *S aureus* transmission.

Each year, sampling will take place over the same 4-month period in residences, businesses, and at multiple public locations within the main cities of Yuma County, Arizona.

Recruitment and Sampling Processes

After consultation with community partners and local residents, we designed the recruitment and sampling process to take advantage of available community resources. The recruiters were identified and trained (as a cohort) as part of a required undergraduate social work research methods class. A total of 28 bilingual recruiters were provided with basic research design training, ethics training (Collaborative Institutional *Training* Initiative and face to face), recruitment role playing, technology (computer-assisted data entry) training, and biosample collection procedures, with monitoring and follow-up by course instructors and project staff. This process provided the opportunity to target specific sized groups, ethnic makeup, and geographical coverage of sampling. Table 1 identifies the targeted social group size, the number of groups of each size to be targeted, and the breakdown of groups to be recruited by each recruiter/consenter/interviewer. CA- *S aureus* infections peak after the hottest months of the year [34-36]; however, neither agricultural workers nor seasonal visitors are in Yuma at this time. Consequently, the time frame for our sampling was during late winter. Our anticipated sample size is not reliant on sampling when carriage rate is predicted to be highest.

Each recruiter was assigned to recruit a total of 12 social groups, stratified as one-third non-Hispanic white groups and two-third Hispanic groups. The total targeted individual recruitment, based on group size, was 1512. Both group and individual sample sizes had appropriate power, based on an *a priori* power analyses to detect differences of 15% in carriage rate (if one truly exists) and important predictor variables for transmission.

Table 1. Targeted sampling framework for social network and community biosamples.

Variable	Social group size								Total
	2	3	4	5	6	7	8	9	
Number of groups per recruiter	3	3	1	1	1	1	1	1	12
Total groups targeted	84	84	28	28	28	28	28	28	336
Total individuals targeted	168	252	112	140	168	196	224	252	1512

Results

Baseline Effort

The recruiters were able to effectively recruit targeted groups in both residential (mostly family, friends, and neighbors), and public locations (work, school, and public access areas). A total of 2 of the interviewers were not able to complete any viable interviews. From YRMC, we collected 660 clinical isolates associated with SSTIs.

We will characterize *S aureus* infection and carriage rates and compare circulating pathogen genotypes with those associated with disease isolated from local clinical specimens across full-time and part-time resident groups and across Hispanic and non-Hispanic white ethnic groups. Positive samples will be sequenced and compared through phylogenetic analyses with genomes from infection specimens collected at the YRMC to determine if the diversity of the clinical pathogen genotypes is representative of the diversity of strains carried within the general population. In addition, we will determine if clinical and community strains are clustered by ethnicity and thus could partially explain discrepant likelihoods of *S aureus* infections.

Quality Control Processes

The baseline/pilot protocol incorporated a systematic data quality control mechanism including (1) interviewer training and reinforcement of fidelity to the data collection protocol and (2) review of geolocation to assess the spatial distribution of recruited groups and individuals, quality of upload and data integrity of transmitted data, as well as group and one-on-one follow-up on protocol and data integrity review at the end of the field cycle for both survey and biological data collection. The systematic review identified several problems that have subsequently been addressed through quality control measures. A total of 2 of the interviewers provided suspect and unverifiable data, which was subsequently removed from the dataset. A total of 2 other interviewers failed to upload a revised version of the data collection instrument. Those datasets were tagged and cleaned/noted for appropriate analysis. Another interviewer collected answers to each question but deviated from the protocol by entering responses for the participant. As this was not approved, those data were eliminated from the overall dataset. After excluding cases (n=70) from the above interviewers, we recruited a total of 335 groups (group size: 2=89, 3=79, 4=39, 5=33, 6=24, 7=24, 8=24, and 9=23), which included 1267 individuals (Table 2).

Through our postdata collection evaluation, we identified ways in which our interviewer training, the data collection technology, sampling logistics, and data quality monitoring protocols could be improved. Data collection occurred using the Survey123 app (ArcGIS) on Samsung Galaxy Tab A 7.0 tablets. Some respondents had to be assisted with the touchscreen nature of the survey. The geographical location of the tablet at the time of the survey was automatically recorded, but sometimes failed, presumably because of an inability to obtain satellite global positioning system location. User input of geolocation of their residence and work was also inconsistent as these questions could not be set as required by the software and were often inadvertently skipped. In addition, the survey app sometime crashed. No data were lost, and restarting the software returned the respondent to the place where they left off but was an inconvenience. The integrated survey123 barcode scanner was slow and ineffective. We used a separate barcode scanner to read the group identity document (ID), which was then be copied and pasted into the survey to link data from individuals within a group as well as link survey and biological data. Due to this extra step, surveyors often manually entered group ID information that sometimes introduced errors. For some respondents, there was confusion over the letter designation scheme we used to identify individuals within each group, causing erroneous data on individual relationships within each group. On the basis of this feedback and review of data, future interviews will be administered in paper and pencil format. Such a change allows group data to be collected in a timelier manner (no need to wait for an available tablet), requires less assistance from interview staff, eliminates software glitches, and provides a hard copy backup once data are entered. Additional confusion can be greatly reduced in the new data collection protocol by improved explanations, training, and formatting of the revised instrument. We used the protocols established by Biemer [37] to identify additional ways in which to ensure and improve data accuracy, credibility, usability, relevance, accessibility, and completeness.

The quality control screening excluded a substantial proportion of year 1 data. This screening included checks to ensure the correct number of respondents in each group as well as checks for within-group response consistency and social relationship fidelity (eg, correct self-identification and mutually consistent kin and spouse identification). These exclusions ensure social group integrity and are tracked as per STROBE guidelines [37]. There were 168 groups encompassing 633 individual respondents after this quality control screening.

Table 2. Baseline demographic, economic, and social characteristics of Yuma pilot year 1 data.

Participant characteristic	Value[a]
Age[b] (years), mean (SD)	28.1 (14.2)
Sex, n (%)	
Female	384 (60.7)
Male	289 (39.3)
Race, n (%)	
White	330 (52.1)
Black	37 (5.9)
No preferred race	139 (22.0)
Other race only	70 (11.1)
Multiracial	57 (9.0)
Ethnicity, n (%)	
Hispanic	172 (27.2)
Non-Hispanic	461 (72.8)
Educational level, n (%)	
Less than high school	305 (48.2)
High school	114 (18.0)
Some college	142 (22.4)
College graduate or higher	72 (11.4)
Employment status, n (%)	
Employed	350 (55.3)
Retired	11 (1.7)
Not currently working	26 (4.1)
Homemaker	17 (2.7)
Student	164 (25.9)
Missing	65 (10.3)
Home tenure, n (%)	
Own home	286 (45.2)
Rent/other arrangement	347 (54.8)
Self-rated health, n (%)	
Poor/fair	70 (11.1)
Good	258 (40.8)
Very good	185 (29.2)
Excellent	79 (12.5)
Missing	41 (6.5)
Social group size, n (%)	
2	102 (16.1)
3	162 (25.6)
4	64 (10.1)
5	80 (12.6)
6	60 (9.5)
7	49 (7.7)

Participant characteristic	Value[a]
8	80 (12.6)
9	36 (5.7)

[a]Some percentages do not sum to 100 because of rounding.

[b]One value of age was missing.

Year 2: Revised Data Collection Protocol

The review processes resulted in improvements for year 2 data collection efforts. We now describe our revised protocol that is designed to eliminate the previously discovered threats to data integrity and provide a more transparent and traceable data collection process.

Recruitment and Consenting

We will continue to use "culturally congruent recruiters" to manage the quality of interview and refusal rate. Working with our community partners, we are implementing a broader community matched configuration for recruitment for our consenters and interviewers. To the extent possible, the demographic characteristics (age, gender, ethnicity, and language preference) of the interview teams will match the demographic characteristics of the target population.

Recruiter Training

Recruiters receive a combination of didactic, hands-on, and role playing training (approximately 8 hours), followed by a minimum of 3 supervised field-based data collection sessions (approximately 8 hours), with direct feedback on all aspects of recruitment, data collection, and data transmission. All data collection sessions are then monitored for a minimum of 1 month, with periodic checks and problem solving debriefing each week. The didactic training comprises an overview of the project (both theory and hypotheses), introduction to recruiting principles and scripts, questionnaire details, biological sampling, and ethical (institutional review board) considerations. The hands-on elements include practice delivering scripts and answering anticipated participant questions. This element is followed by role playing to practice recruiting, informed consent, biological sample collection, and questionnaire delivery using other trainees and staff to work through the data collection process. Once the principal investigator and investigators are satisfied with data collection competency, the recruiters take part in at least 3 separate recruitment events with procedural review before each event and full debriefings after each group is recruited and provides data. All data are collected by 2-person recruiter teams to preserve data collection integrity. Weekly debriefings to resolve any unanticipated problems are conducted by supervising staff.

Sample Size and Sampling Plan

We will continue to use a stratified purposive sampling approach to capture socially associated groups at both private and public events and venues in Yuma County. Each year, we aim to recruit 370 groups with a target of 243 Hispanics and 122 non-Hispanic whites. This will give us the power to detect a 15% difference in carriage rates. We will enroll naturally occurring social groups that will likely include family, friendship, work, and neighbor relationships. Such sampling will thus produce a wide variety of types of social contacts of varying closeness and strength.

Inclusion and Exclusion Criteria

Our recruitment process is aimed at capturing local migrant laborers as well as part-time winter residents but excluding groups consisting of only tourists as they are less likely to reflect local *S aureus* carriage rates but may contribute to transmission within a social group. The use of a proxy to respond to the survey for nonliterate children as well as the person ID for the proxy within the group will be recorded. Any individual younger than 6 months will be excluded. Our aim is to sample a representative section of the community. We will, therefore, not specifically target at-risk groups to avoid biasing our estimation of carriage within the general population. In addition, our projected sample size is based on a power analysis using the carriage rate of the general population and should provide a sufficient number of positive samples to address our questions without targeting at-risk groups.

On the basis of data captured, cleaned, and preliminarily analyzed during the pilot (year 1), the number of groups to be recruited in different venues is listed in Table 3.

Each consented individual will be asked to respond to the *S aureus* data collection instrument and will be swabbed (anterior nares, throat, and hand) to detect both MSSA and MRSA colonization. The *S aureus* cultures will go through whole genome sequencing to determine phylogenetic relationships. Such analyses will enable us to identify cases of likely transmission within a group. Genomic comparisons to be compared with *S aureus* MSSA and MRSA clinical isolates collected from YRMC will allow us to determine if the clinical strains are a representative subset of those circulating in the community.

Table 3. Year 2 targeted group recruitment for Yuma County.

City	Public spaces, n		Public events, n		Private spaces, n		Total groups (N=370)
	A[a] (n=56)	H[b] (n=112)	A (n=56)	H (n=112)	A (n=31)	H (n=62)	
Yuma	50	75	50	75	26	38	314
Somerton	2	4	2	4	2	4	18
San Luis	4	9	4	9	4	8	38

[a]A: Non-Hispanic white groups recruited.

[b]H: Hispanic groups recruited.

Variables

This paper and pencil survey consist of 33 items with an additional 7 items on relationship for each person within the group. We collect basic demographic information, health status, alcohol use, level of contact (physical and social), and identification of social relationships within the group. We include a general measure of health as there is evidence that *S aureus*, colonization is associated with health disparity indicators such as poor health status [38-41]. We also assess educational attainment and home ownership given that *S aureus* colonization may also be associated with socioeconomic status [14]. We will, therefore, use well-tested variables that permit partitioning of the relative potency of ethnic versus socioeconomic determinants of colonization [42]. The social integration measures predict morbidity and mortality [43,44] including increased susceptibility to infectious diseases [45]. Some of these factors have previously been shown to be important for determining likelihood of infection and will be used with ethnicity to determine the best predictors of colonization. The source variables include demographic questions from the US National Health Interview Survey (NHIS; gender, age, ethnicity, income, education, and employment); general health, including history of infections and antibiotic use; and health care access, including location of health care services; questions identified as risk factors for CA-MRSA transmission risk (number of people in household and contact with animals). The US NHIS items have validated Spanish language translations [46]. We also assess perceived strength of physical contacts between members of the social group with contact defined as either direct physical contact that would increase the probability of *S aureus* transmission, or indirect physical contact through shared contact items or conditions [34]. Each individual in a social group is asked to complete background information about themselves and afterward answer 7 questions about each member of their group regarding the nature and intensity of their contacts (ie, type of relationship: romantic partner, parent, sibling, friend, coworker, etc, closeness of relationship, amount of physical contact, frequency of social contact, shared meals and living space, and shared pets). The composite network data will provide data on individual connectivity. Macro-level social networks will be assessed with the Social Network Index [45], which is predictive of susceptibility to infection [45] and captures social integration features associated with mortality [47]. Added to this index are other social contact questions assessed in US public health surveys that are also predictive of hard health end points [43,48]. The entire data collection instrument has been translated into Spanish following World Health Organization–recommended protocols that include translation-back translation and cognitive debriefing [49,50]. We also checked the linguistic phrasing of the instruments for local vernacular.

The social network and social determinants data collection instrument will be integrated with biological data instrumentation such that data are collected concurrently.

Biological Data Collection

After recruitment and consent, participants are directed to provide biological samples before answering survey questions on the data collection instrument. This workflow is designed to minimize the possibility of cross-contamination of participant and researcher microbes. Sample collection kits are prepackaged and prelabeled such that a gallon-sized Ziploc bag is labeled for a group and contains quart-sized Ziploc bags labeled for each individual within a group. The “group” bag also contains gift cards (as incentives) and name-tag stickers written with “A,” “B,” “C,” etc, depending on the number of people within the group. These name tags and naming scheme allow for the maintenance of anonymity as respondents answer questions about their relationships within a group. Each “individual” bag (all within the “group” bag) contains 6 prelabeled BBL CultureSwabs. Swab labels include participant IDs as well as the body site to be sampled. Prelabeling and packaging of culture swabs is done aseptically (using nitrile gloves followed by a wipe down with ethanol) to prevent contamination with microbes from the preparing laboratorian. Nesting the “individual” bags within the “group” bag also eliminates the need for the field researchers to handle swabs as individual participants handle and open their own bag.

After opening the group bag, researchers pass out the prefilled name tags while explaining that the letter on the name tag is the identifier for each person within the group. “Individual” bags are then distributed, and respondents are instructed to remove a specific color-coded prelabeled swab. All participants are then guided through swab handling and swabbing methods. To further ensure consistent sampling, the researcher counts off 20 seconds while instructing participants to continue swabbing and turning the swab for each body site (palm, nose, and throat). The palm of only 1 hand is swabbed, but for the nose, both nares are swabbed for 10 seconds each. After each swab, the researcher holds out the empty “group” bag for participants to drop the used swab into. When all swabs are completed and collected, researchers seal the “group” bag and push on both ends of the bag to ensure that all swabs are completely closed within the bag. Bags containing used swabs are stored in a cool place for

as short of a time period as possible before placing them on ice or in a refrigerator at approximately 4°C. After sample collection, participants are provided with the survey, which typically takes approximately 12 to 15 min for the group to complete, based on timed interviews in the field.

Biological samples are transported to our laboratory on the NAU-Yuma campus where the swabs are stored at 4°C before streaking on CHROMagar Staph aureus plates. These plates are specific to Gram-positive organisms and contain chromagens that turn *S aureus* colonies fuchsia for easy and accurate identification. Plates are read after 24 to 26 hours of incubation at 37°C. For samples that are determined to be positive for *S aureus*, selected growth is scraped off the plate and placed into cryogenic vials containing 20% glycerol for long-term storage at –70°C for subsequent culturing and isolation, DNA extraction, and whole genome sequencing at the NAU flagstaff campus.

Quality Control Processes

Given the success and importance of the systematic data quality control mechanisms implemented during the baseline/pilot data collection, we have instituted a more comprehensive protocol for ensuring data quality. Surveyor training now includes additional discussions of questionnaire content, role-playing, and supervised data collection in the field. Immediate review of surveys in the field now allows for the identification of common errors and a discussion with the surveyors on mitigation of such errors.

Discussion

Our study will examine carriage, pathogen genotypes, clinical versus community strains of *S aureus* and the impact of social relationships and shared physical environments on carriage. Our study will also utilize genomic analysis to infer transmission patterns across social and geographic environments and distinguish between antibiotic resistant and susceptible *S aureus* subtypes. These complementary approaches should provide a better understanding of *S aureus* transmission and inform more robust infectious disease intervention and prevention strategies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from NIH.
[PDF File (Adobe PDF File)457 KB - resprot_v8i9e14853_app1.pdf]

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Abbreviations

CA: community-acquired
HA: health care–acquired
ID: identity document
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-sensitive *Staphylococcus aureus*

NAU: Northern Arizona University
NHIS: National Health Interview Survey
SSTI: skin and soft tissue infection
YRMC: Yuma Regional Medical Center

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Protocol

The Influence of Beta-2 Adrenergic Receptor Gene Polymorphisms on Albuterol Therapy for Patients With Asthma: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Albuterol is one of the most frequently used medications in clinical practice and seeing varying responses to albuterol between individuals is not uncommon. Multiple studies have been conducted to investigate the associations of differing responses due to albuterol, particularly with regards to the two nonsynonymous single nucleotide polymorphisms (SNPs) at positions 16 (Arg16Gly: substitution of arginine to glycine at position 16; rs1042713) and 27 (Glu27Gln: substitution of glutamic acid to glutamine at position 27; rs1042714) on the β-2 adrenergic receptor (ADRB2) gene. However, the directions of the correlations are conflicting.

Objective: The objective of this systematic review and meta-analysis is to assess the effect of the two SNPs on the ADRB2 gene, in terms of the responses that present in asthmatic patients shortly after albuterol inhalation.

Methods: The primary outcome of this work is a detailed study of the associations of the two SNPs in the ADRB2 gene with treatment response and lung function testing shortly after administration of albuterol to asthmatic patients. A comprehensive literature search, using the OVID platform, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, will be conducted by a specialized librarian without language restrictions. We will include both prospective and retrospective original observational studies, and we will exclude nonhuman or in vitro studies. All abstracts will be reviewed by two authors who will also individually perform data extraction from each eligible study. Any arising disagreements will be resolved through discussion with a third party. Risk of bias for all included studies will be independently assessed using the quality of genetic association studies tool. We will report the systematic review and meta-analysis, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A narrative synthesis of study results or meta-analyses will be undertaken when appropriate.

Results: At the moment of writing, we have already started the preliminary literature search and piloting of the study selection process. The anticipated completion date is September 30, 2019.

Conclusions: Our systematic review and meta-analysis aims to clarify the current evidence of associations between the two nonsynonymous SNPs in the ADRB2 gene and the responses that present in asthmatic patients shortly after albuterol inhalation. If positive correlations are found, this knowledge may be used to improve personalized pharmacotherapy of albuterol use.

Trial Registration: PROSPERO CRD42019074554; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=74554

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KEYWORDS

pharmacogenomics; polymorphisms; ADRB2; albuterol; asthma; response

Introduction

Albuterol is one of the most commonly used medications in current practice. According to the 2017 Quintiles IMS National Prescription Audit, albuterol is ranked 9th in terms of number of times dispensed in the US market, with 70 million prescriptions in 2016 [1]. Albuterol is a β-2 adrenergic agonist and is used for patients who develop bronchospasm due to conditions such as asthma, chronic obstructive lung disease, and cystic fibrosis [2,3].

Albuterol works by activating β-2 adrenergic receptors on airway smooth muscles, leading to the activation of adenylcyclase and to an increase of cyclic-3', 5'-adenosine monophosphate (cAMP) in the cells [3,4]. These increased cAMP levels then activate protein kinase A, which inhibits the phosphorylation of myosin and lowers the concentrations of ionic calcium in the cells, thus resulting in the relaxation of airway smooth muscles. In addition, the increased levels of cAMP inhibit the release of mediators from mast cells in the airway. Various kinds of adverse drug reactions occur due to albuterol, including headaches, tachycardia and dizziness, and reported frequencies of these events appears to be greater than 3.0% [3]. Albuterol causes cardiac effects by stimulating β-2 adrenoceptors and by activating peripheral receptors, but it also causes dizziness by stimulating skeletal muscle β-2 adrenoceptors [5,6].

Clinically, the response to albuterol is measured by physical examination with auscultation but forced expiratory volume in the first second (FEV1) can also be used in order to determine both response and reversibility of airflow obstruction after inhalation of albuterol. Reversibility can be measured by observing the change in FEV1. Various cutoff levels of positive response to albuterol have been reported, but usually a 12-15% increase is considered to be a meaningful change [7,8].

It is very common for clinicians to experience interindividual variabilities of responses to albuterol that cannot be explained just by age, severity of asthma, or environmental factors. Some studies estimated that 60.6% of interindividual variation in the FEV1 response due to albuterol may be attributed to genetic factors [9-11]. The first pharmacogenomic study of albuterol came out in 1997 [12], and since then, multiple pharmacogenomic research studies related to albuterol response or adverse reactions and β-2 adrenergic receptor polymorphisms have been reported, most of which have focused on the β-2 adrenergic receptor (ADRB2) gene that is located on chromosome 5q31-q32 and encodes β-2 adrenergic receptors [13]. These studies mainly investigated two polymorphic loci in the ADRB2 gene, including nonsynonymous variants such as Arg16Gly (substitution of arginine to glycine at position 16; rs1042713) and Glu27Gln (substitution of glutamic acid to glutamine at position 27; rs1042714), the minor allele frequencies of which are reported to be 48% for Arg16Gly and 20% for Glu27Gln per 1000 genomes among individuals, according to the Phase 3 Genomes Browser [14]. These two variants were originally reported to be associated with the development of other types of asthma, such as nocturnal asthma, and also with agonist-promoted downregulations by isoproterenol in the in vitro studies [15,16]. The in vitro functional study of those mutations showed that the Arg16Gly mutation had a higher degree of agonist-promoted downregulation of β-2 adrenergic receptor expression after 24 hours of exposure of beta-stimulant [16]. Subsequently, Martinez et al first showed the association of positive response for patients carrying Arg-16 due to albuterol, and they also showed a strong linkage disequilibrium between the two polymorphisms (Arg-16 and Gln-27 alleles) [12]. Another in vitro study also reported these associations by using human airway smooth muscle cells, suggesting that the Gly-16 allele is associated with enhanced downregulation of β-2 adrenergic receptors in transformed cell lines [17]. These in vitro studies could explain the mechanisms of these polymorphisms, in particular a possibility of change in function of β-2 adrenergic receptors which has since been corroborated by other studies [18-22]. However, there are also multiple studies that have showed conflicting results about associations between responses due to albuterol and these polymorphisms, with some showing better response in patients with Gly-16 and others showing no associations with either of these two SNPs [23-29].

Despina et al attempted to conduct a systematic review of these associations back in 2006, but finally decided to abandon this work after concluding that the reported studies were too heterogeneous to standardize and synthesize for systematic review [30]. Subsequently, Finkelstein et al conducted a meta-analysis in 2009, showing positive correlations in asthmatic children with the Arg/Arg genotypes at position 16 of the ADRB2 gene (odds ratio [OR] 1.77; 95% CI 1.01-3.1; P=.03), compared with the Arg/Gly or Gly/Gly genotypes [31]. They did not find any positive correlations at position 27 of the ADRB2 gene (OR 1.04; 95% CI 0.76-1.42). They successfully completed the meta-analysis, specifically limiting the target populations and phenotypes to asthmatic children and albuterol responders and defining being responsive as an increase of FEV1 by 15%. However, there are multiple limitations in the meta-analysis, most notably that they did not follow the principles of the Cochrane Handbook for Systematic Reviews of Intervention or the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32,33]. In addition, they did not conduct an assessment of risk of bias, nor did they show the results of testing for heterogeneity using the I^2 statistic. Third, this study excluded the investigations of the associations in adult populations, and the studies in which being responsive was defined as an increase of FEV1 by 12% to 15.3% [18,26]. Thus, we cannot definitively rule out the possibility that this study is not an accurate summary of the current evidence for these associations. Since then, more

pharmacogenomic studies have been performed for these associations; however, no systematic reviews or meta-analyses that included adult populations have yet been published.

Clinical practice should only be revised after careful and thorough critical review of published studies. Systematic reviews and meta-analysis are currently considered to be the highest levels of evidence and therefore would be sufficient to inform a change in current medical practice [34]. Key to the success of this project will be the focus on study data that relates to specific phenotypes due to one drug only, minimizing heterogeneities and maximizing inclusion of previous studies. Our aim will be to clarify the current records of pharmacogenomics studies that focused on albuterol, and whether the ADRB2 genetic polymorphisms have any influence on responses that present in asthmatic patients shortly after albuterol therapy, then to share our findings with clinicians in order to escalate consideration of incorporating these findings into actual medical practice.

Methods

Overview

We will perform a systematic review and meta-analysis based on the principles of the Cochrane Handbook for Systematic Reviews of Intervention [32]. The report of the systematic review and meta-analysis will follow the PRISMA statement [33], and current protocol follows the 2015 PRISMA Protocol (see Multimedia Appendix 1) [35].

Primary Outcome

In this study we will include asthmatic patients of any age group who are also on albuterol therapy, and we will study the responses of ADRB2 variant-type allele carriers to compare these responses to asthmatic patients carrying the ADRB2 wild-type allele. The study outcomes will be associations of Arg16Gly (rs1042713) and Glu27Gln (rs1042714) polymorphisms in the ADRB2 gene with treatment response and lung function testing (FEV1) shortly after administration of albuterol.

Search Strategy and Sources

A comprehensive literature search using the OVID platform will be performed by a specialized librarian in order to identify the relevant studies from our respective inception date to completion date, without any special date limits, and using the following electronic databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. No language restrictions will be applied. The literature search strategies will be created using medical subject headings and text words related to “albuterol” AND “ADRB2 gene” AND “asthma”. Various synonyms and related terms for all subjects will be used. Abstracts and conference reports will be included, and articles will also be identified from reference lists, and upon identification of relevant studies the reviewers will check for additional relevant cited, and citing, articles. This search strategy is outlined in more detail in Multimedia Appendix 2.

We registered this protocol on the International Prospective Register of Systematic Reviews on January 24, 2019 (registration number: CRD42019074554). When any amendments are required, we will provide the following information: date of each amendment, description of changes, and rationale for changes. We will include those changes in the protocol.

Eligibility Criteria

We will include both prospective and retrospective original studies that meet the following criteria: (1) They are observational (cohort, cross-sectional or case-control) studies with control groups, or randomized controlled trials, on asthmatic patients on albuterol therapy; (2) Arg16Gly (rs1042713) and Glu27Gln (rs1042714) polymorphisms in the ADRB2 gene were reported; and (3) short-term differences in change of percentage of FEV1 after albuterol inhalation are reported for relevant genotypes.

We will exclude nonhuman or in vitro studies (experimental), case reports, case series, reviews, editorials, newsletters, commentaries, abstracts, conference reports, and original studies that did not report outcomes of interest. We will exclude studies in which no albuterol, or its equivalents, were used, or no Arg16Gly (rs1042713) or Glu27Gln (rs1042714) polymorphisms in the ADRB2 gene were identified. Duplicated studies will also be excluded.

Data Collection and Analysis

Studies of patients, regardless of their age, sex, ethnicity, body weight, height, smoking status, duration of asthma, severity of asthma, use of concurrent drugs, and co-morbidities, will be included.

We will extract the eligibility information for each study pertaining to study identification (first author, year of publication, and country where patient recruitment took place), study design, patient population (number of enrolled patients, age, gender, predominant ethnicity, concomitant drug use, smoking status, severity of asthma, co-morbidities, subjects’ genotype of ADRB2 gene), brand or generic name of albuterol, dose of albuterol, whether or not methacholine provocation was conducted, timing to measure lung function testing, genotyping methods, allele frequencies, and results of lung function testing for each genotype of ADRB2. Studies or articles retrieved from all databases will be imported into EndNote. Titles and abstracts of all studies retrieved as a result of the search, as well as those from additional sources, will be screened independently by two review authors (KH and SK) to identify studies that potentially meet the inclusion criteria outlined above. After obtaining full-text versions of all potentially eligible studies, two review team members (KH and SK) will independently assess them for eligibility. Both reviewers will be independently involved in all stages of study selection, data extraction, and risk of bias assessment. Any disagreement between reviewers regarding the eligibility of particular studies will be resolved through discussion with a third independent reviewer (TK). Where studies are duplicated, we will use the study that had the largest number of patients. We will contact the original authors of the studies for missing data by e-mail, when required.

Risk of bias for all included studies will be independently assessed by two reviewers (KH and SK) using the quality of

genetic association studies (Q-Genie) tool [36]. This tool, containing 11 items, was developed using the Strengthening the Reporting of Genetic Association Studies and Strengthening the Reporting of Genetic Risk Prediction Studies guidelines [37,38]. The Q-Genie tool has a 7-point scale, rating and classifying 1 and 2 as low, 3 and 4 as moderate, and 5–7 as high. The overall quality of the study is classified by the total score from each question, indicating poor quality if scores ≤35, moderate quality if scores >35 and ≤45, and good quality if scores >45. We will also check for departure from Hardy-Weinberg equilibrium using Michael H. Court's online calculator [39]. Any disagreement between the review authors will be resolved by consulting with a third reviewer (TK). If necessary, we will contact the original authors of the studies for assistance with clarification of any identified discrepancies. Potential publication bias will be analyzed through the use of a funnel plot and the Egger test.

Data will be analyzed by RevMan 5.3 [40], and characteristics of included studies will be described. A narrative synthesis of study results will be undertaken, including evidence tables and forest plots to aid in data presentation when appropriate. When there is missing data, we will attempt to contact the original authors of the study to obtain the relevant missing data. Where appropriate, imputation methods will be used if missing data cannot be obtained [41]. Meta-analysis of results will be performed if sufficient clinical and statistical data is available, and in that case, individual study results will be pooled (with weights based on the inverse variance method) when two or more studies have similar study designs and have usable data for the outcomes of interest. We will then pool all the results using a fixed effect or random effects meta-analysis. The types of summary statistics considered in the meta-analyses will be standardized mean differences for continuous outcomes and pooled risk ratios or odds ratios for binary outcomes, with 95% CI and two-tailed *P* values for each outcome, based on the following genotypes: Arg/Arg, Arg/Gly and Gly/Gly for Arg16Gly, and Glu/Glu, Glu/Gln, and Gln/Gln for Glu27Gln. *P* values<.05 will be considered significant overall associations of the two polymorphisms, with change of percentage of FEV1 shortly after albuterol use.

Measures of heterogeneity of effect for different studies will be evaluated using the I^2 statistic and Chi-squared test, when possible. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity, but if study estimates have small or moderate heterogeneity they will be combined using a DerSimonian and Laird random effects model. When systemic narrative synthesis is performed, it will cover the information presented in the text and tables that is sufficient enough to summarize and explain the characteristics and findings of the included studies.

Publication bias will be examined based on visual inspection of a funnel plot, with mean differences plotted on the x-axis and inverse of variance of the effect plotted on the y-axis.

If the necessary data is available, we will carry out subgroup analyses based on age, year of publication, sample sizes, and whether bronchoconstriction was provoked by methacholine or not. We will also conduct sensitivity analyses to assess heterogeneity, according to quality components and risk of bias, by omitting one study at a time and calculating a pooled effect size for the remaining studies.

Results

Preliminary literature search and piloting of the study selection process has been started and is anticipated to be completed by September 30, 2019.

Discussion

We will perform a systematic review and meta-analysis and currently do not anticipate any issues with the implementation of the proposed protocol. A key part of our strategy is to exclusively focus on specific phenotypes due to a certain drug, thus decreasing heterogeneities. Our findings will clarify the current status of pharmacogenomics studies of albuterol response and uncover the limitations of current evidence that are preventing clinical implementation of these findings in actual clinical practice. The work may also facilitate further research and continued accumulation of further evidence for these associations, and if positive correlations are found it could potentially help clinicians to provide more personalized medicinal care for their patients.

Authors' Contributions

All authors created the study design. KH and TK developed the search strategy with the librarian. KH, SK and TK performed the writing. EO and TM performed the critical revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P 2015 Checklist.
[DOCX File, 31KB - resprot_v8i9e14759_app1.docx]

Multimedia Appendix 2
Search terms and strategies.

[DOCX File, 17KB - resprot_v8i9e14759_app2.docx]

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Abbreviations

Arg: arginine
cAMP: cyclic-3', 5'-adenosine monophosphate
FEV1: forced expiratory volume in the first second
Gln: glutamine
Glu: glutamic acid

Gly: glycine
OR: odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Q-Genie: quality of genetic association studies

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Protocol

Investigating the Relationship Between Resilience, Stress-Coping Strategies, and Learning Approaches to Predict Academic Performance in Undergraduate Medical Students: Protocol for a Proof-of-Concept Study

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Abstract

Background: The evolution of an undergraduate medical student into an adept physician is perpetual, demanding, and stressful. Several studies have indicated medical students have a higher predominance of mental health problems than other student groups of the same age, where medical education acts as a stressor and may lead to unfavorable consequences such as depression, burnout, somatic complaints, decrease in empathy, dismal thoughts about quitting medical school, self harm and suicidal ideation, and poor academic performance. It is imperative to determine the association between important psychoeducational variables and academic performance in the context of medical education to comprehend the response to academic stress.

Objective: The aim of this proof-of-concept study is to determine the relationship between resilience, learning approaches, and stress-coping strategies and how they can collectively predict achievement in undergraduate medical students. The following research questions will be addressed: What is the correlation between the psychoeducational variables resilience, learning approaches, and stress-coping strategies? Can academic performance of undergraduate medical students be predicted through the construction of linear relationships between defined variables employing the principles of empirical modeling?

Methods: Study population will consist of 234 students registered for the MBBS (Bachelor of Medicine, Bachelor of Surgery) at Mohammed Bin Rashid University of Medicine and Health Sciences distributed over 4 cohorts. Newly registered MBBS students will be excluded from the study. Various psychoeducational variables will be assessed using prevalidated questionnaires. For learning approaches assessment, the Approaches and Study Skills Inventory for Students questionnaire will be employed. Resilience and stress-coping strategies will be evaluated using the Wagnild-Young resilience scale and a coping strategies scale derived from Holahan and Moos's Coping Strategies Scale, respectively. Independent variables (resilience, stress-coping strategies, and learning approaches) will be calculated. Scores will be tested for normality by using the Shapiro-Wilk test. An interitem correlational matrix of the dependent and independent variables to test pairwise correlation will be formed using Pearson bivariate correlation coefficients. Regression models will be used to answer our questions with type II analyses of variance in tests involving multiple predictors. Regression analyses will be checked for homogeneity of variance (Levine test) and normality of residuals and multicollinearity (variance inflation factor). Statistical significance will be set at 5% (alpha=.05). Effect sizes will be estimated with 95% CIs.

Results: Psychoeducational instruments in the form of validated questionnaire have been identified in relation to the objectives. These questionnaires have been formatted for integration into Google forms such that they can be electronically distributed to the consenting participants. We submitted the proposal to MBRU institutional review board (IRB) for which exemption has been awarded (application ID: MBRU-IRB-2019-013). There is no funding in place for this study and no anticipated start date. Total duration of the proposed research is 12 months.

Conclusions: Psychoeducational instruments used in this study will correlate resilience, stress-coping strategies, and learning approaches to academic performance of undergradudate medical students. To the best of our knowledge, no study exploring the multidimensional association of key psychoeducational variables and academic performance in undergraduate medical students has been pursued. Investigated variables, resilience, learning approaches, and stress-coping strategies, are individual traits, however; students' learning history before they joined MBRU is unknown, so our research will not be able to address this specific aspect.

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KEYWORDS

medical education; undergraduate medical education; psychological resilience; resilience; learning; coping behavior; psychological stress

Introduction

Background

The evolution of an undergraduate medical student into a safe and competent physician is interminable, demanding, and stressful [1]. This journey involves combatting what Smith [2] defined as the "swampy lowlands where situations are confusing 'messes' incapable of technical solutions" coping with hidden insecurities of clinical practice. In fact, medical students have a higher predominance of mental health problems than other student groups of the same age [3]. This indicates that medical education itself contributes as a key stressor, an observation corroborated by other studies [4,5]. Academic stress is defined as the body's response to academic-related strains and tensions that exceed adaptive potentials of students. Medical students experience high degrees of academic stress, where the most commonly reported stressors in the academic environment are related to oral presentations, academic overload, scarcity of time to meet commitments, and taking examinations. [6]. While some academic stress may boost academic performance [7], elevated stress levels in medical students may lead to detrimental consequences such as depression [8], burnout [9], somatic complaints [10], decrease in empathy [11], dismal thoughts about quitting medical school [12], suicidal ideation [5], and poor academic performance [13,14]. Therefore, it is imperative to determine the association between important psychoeducational variables and academic performance in the context of medical education to define the role of each psychoeducational variable in the response to academic stress.

Aim

The aim of this proof-of-concept study is to determine the relationship between meta-motivational skills for handling stress (resilience), meta-cognitive skills for study (learning approaches), and meta-emotional skills for managing stress (stress-coping strategies) and how they can collectively predict achievement in undergraduate medical students, founded on the competence of learning, studying, and performing under stress (CLSPS) model [15] (Textbox 1).

Research Questions

The following research questions will be addressed:

- What is the correlation between the psychoeducational variables resilience, learning approaches, and stress-coping strategies in an undergraduate entry medical program?
- Can academic performance of undergraduate medical students be predicted through the construction of linear relationships between the defined variables employing the principles of empirical modeling?

Hypotheses

The research questions are founded on the following hypotheses regarding undergraduate medical students:

- Resilience is correlated positively with strategic and deep learning approaches and negatively with surface learning approaches.
- Resilience is correlated positively with problem-focused stress-coping strategies and negatively with emotion-focused stress-coping strategies.
- Emotion-focused stress-coping strategies are correlated positively with surface learning approaches and negatively with strategic and deep learning approaches.
- Resilience is a positive predictor of strategic and deep learning approaches and a negative predictor of surface learning approaches; in addition, it is a positive predictor of problem-focused stress-coping strategies and a negative predictor of emotion-focused stress-coping strategies. Moreover, resilience together with strategic and deep learning approaches and problem-focused stress-coping strategies will have a positive and a linear relationship with academic performance.

Textbox 1. The competence of learning, studying, and performing under stress model of de la Fuente [15].

Knows (knowledge):

- Facts: knowledge about the characteristics of the class subject or professional exam (career opportunities, percentage of candidates who pass, requirements)
- Concepts: competitive exam system, requirements, type of examination, scoring, prior merits/credits, type of class subject
- Principles: beliefs about the professional exam or selection process

Knows how (skills):

- Principles: beliefs about the professional exam or selection process
- Instrumental skills: written and oral skills
- Learning and study skills: study skills and techniques
- Meta-cognitive skills for study: learning approaches
- Meta-emotional skills for managing stress: coping strategies
- Meta-motivational skills for managing stress: resilience
- Meta-behavioral skills for managing stress: self-regulation strategies

Knows how to be (attitudes):

- Attitudes and values: behavioral confidence, achievement motivation, mindset
- Study habits (time management, persistence, discipline)

Literature Review

Search Strategy

Relevant publications were searched in PubMed using the keywords resilience, learning approaches, stress-coping strategies, academic performance, and combinations and variations of these words in conjunction with PubMed-accepted Boolean operators employing the strategy of Jadad et al [16]. Further, this proposal has drawn from the references listed in the research of de la Fuente et al [17] and Garzon-Umerenkova et al [18].

Meta-Motivational Variable: Resilience

Resilience is "a dynamic process wherein individuals display positive adaptation despite experiences of significant adversity or trauma" [19]. In medical education, resilience has a key role as a motivational-affective variable, where it not only acts as a key impetus for the comprehension of scholastic and individual objectives, it also provides one with suitable strategies to tackle adverse conditions of stress and anxiety [20]. Erudition directed to superior academic performance in medical students not only requires motivation, effectively tackling rhythms, modular stresses, and responses of different types but also the capability to self-motivate to effectively counter taxing and traumatic situations, concurrently avoiding circumstances of exacerbation or poignant distress such as vulnerability, apathy, dejection, or anguish [21-23]. Although considerable research has focused on investigating the factors for resilience in medical education, little research has been conducted to investigate the relationship of resilience with other confounding psychoeducational elements such as stress-coping strategies and learning approaches.

Meta-Emotional Variable: Stress-Coping Strategies

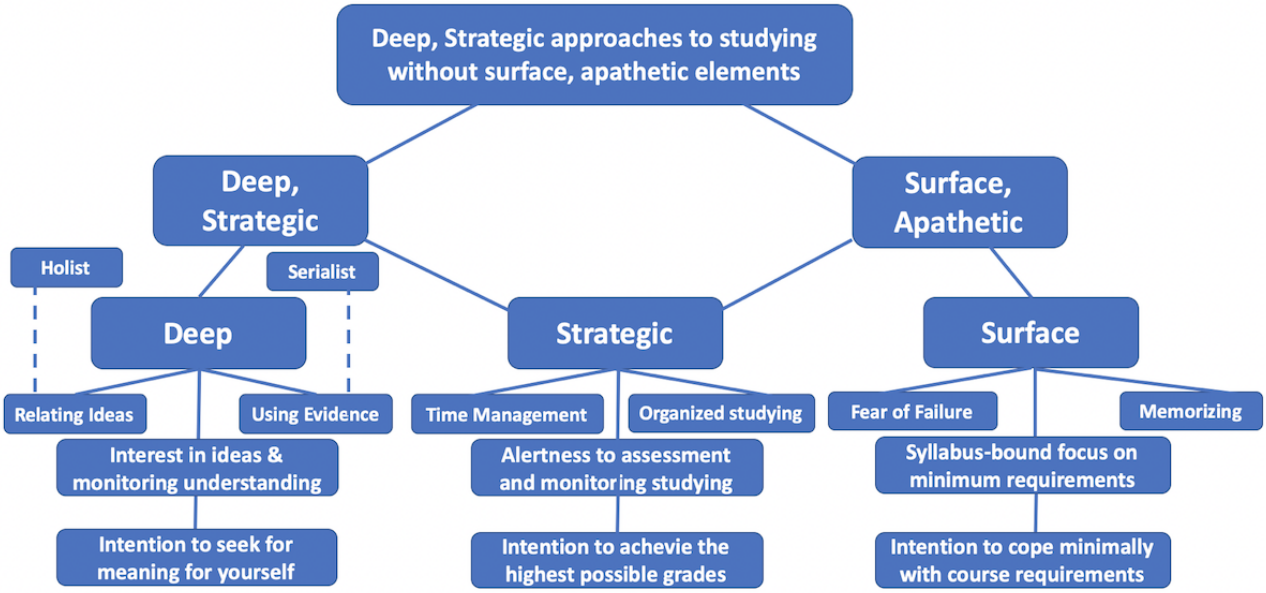
Folkman and Moscowitz [24] define coping as "continually changing cognitive and behavioral practices that are developed to handle specific external and/or internal demands that are valued as beyond the individual's resources." Individuals cope with different traumatic and taxing circumstances in a manner that surpasses the effect of the situational and chronological context, a phenomenon often referred to as coping styles [25]. Intrinsic to these styles is the involvement of a defined thought process and actions defined by Soucy as stress-coping strategies [26]. These can be broadly classified into three types of strategies [27]: problem-focused, emotion-focused, and avoidance-focused.

Although considerable research has been pursued to characterize the coping strategies of medical students, including a 10-year longitudinal study to predict how coping strategies inform styles of success in medical careers [28], there is a dearth of studies investigating how stress-coping strategies can predict academic performance in a multidimensional milieu (in association with resilience and learning approaches).

Meta-Cognitive Variable: Learning Approaches

Biggs defines learning approaches as "learning processes that emerge from students' perceptions of academic tasks influenced by their personal characteristics" [29]. Entwistle et al [30] describe 3 learning approaches: deep, surface, and strategic [30] (Figure 1). The deep approach characterizes students who intend to seek meaning for themselves as well as relating ideas and using evidence. The strategic approach involves students who intend to excel academically by organized studying in order to achieve the highest possible grades. The surface apathetic approach has the intention of coping with the minimum course requirements and is linked to rote memorizing and a fear of failure [31].

Figure 1. Classification of learning approaches as defined by Entwistle [30].



Preliminary Data From Initial Study

An initial cross-sectional study was pursued at MBRU. The ASSIST questionnaire [30] was circulated to 84 students in the college of medicine. Of the 84 students, 64 responded to the questionnaire. Of the 64 responses, 4 responses were excluded as they were either incomplete or ambiguous. Statistical analysis was conducted on the data obtained from 60 responses. Of these students, 57% (34/60) used a deep learning approach, 16% (10/60) used a strategic learning approach, and 27% (16/60) used a surface learning approach.

Next, we investigated the association of learning approaches with teaching approaches in the 60 responses using logistic regression. In this analysis, responses of 5 students were excluded, as they had equivalent scores in teaching approaches. Among the 55 included students, 71% (39/55) preferred the surface teaching approach and 29% (16/35) preferred the deep teaching approach. Furthermore, strategic learners had a significant positive correlation with perceived academic performance compared with other learners (Figure 2).

This initial study indicated that while the predominant learning approach was deep learning (seeking meaning and critical thinking), the preferred teaching approach was surface teaching. Also, strategic learners perceive themselves to perform better academically (Tables 1 and 2) [32].

Figure 2. Preliminary data showing the frequency of predominant learning approaches classified by predominant teaching approaches.

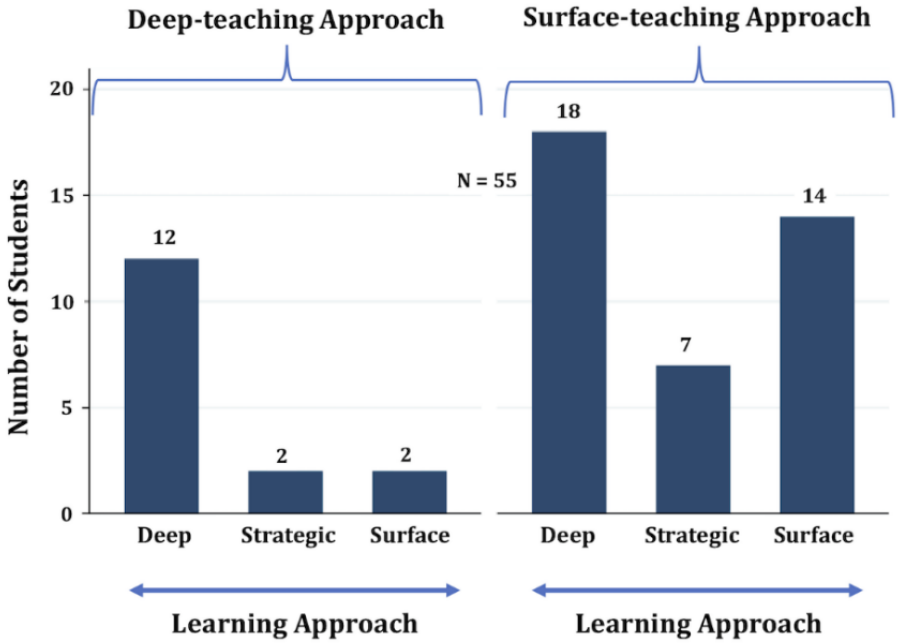


Table 1. Correlation of average learning approach scores and academic performance.

Correlation variable	Strategic score	Surface score	Deep score	Academic performance
Strategic score	__[a]	—	—	—
Surface score	–.08	—	—	—
Deep score	.38	–.32	—	—
Academic performance	.54	–.25	.23	—

[a]Not applicable.

Table 2. *P* values[a] of correlation of average learning approach scores and academic performance.

Correlation variable	Strategic score	Surface score	Deep score	Academic performance
Strategic score	>.99	__[b]	—	—
Surface score	.56	>.99	—	—
Deep score	.003	.01	>.99	—
Academic performance	<.001	.06	.08	>.99

[a]Spearman correlation.

[b]Not applicable.

However, what happens in a multidimensional milieu, when resilience and stress-coping strategies of students are also included, is currently unknown and will be investigated in this study.

Rationale for Proposed Research

In the demanding academic milieu of medical education, the psychoeducational variables resilience, learning approaches, and stress-coping strategies act in concert; it is imperative to investigate the relationships between these variables and their collective effect on the academic performance of undergraduate medical students. To our knowledge this has not been studied, and the proposed research would address this gap.

Methods

Study Landscape

Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU) is a new medical school located in Dubai Health Care City, the health care hub of United Arab Emirates, with a 6-year MBBS (Bachelor of Medicine, Bachelor of Surgery, or *Medicinae Baccalaureus Baccalaureus Chirurgiae*) undergraduate entry medical program where the curriculum is founded on a competency-based educational model. The MBRU curriculum is divided into 3 phases (Figure 3). Each phase of the curriculum includes integrated courses and builds on the preceding one such that the curriculum is a spiral: the students repeat the study of a subject, each time at a higher level of difficulty and in greater depth. The school has a diverse student population, drawing students from more than 19 countries across the globe. Approximately 75% of the students are women.

Participants

As indicated earlier, MBRU is a new medical school in its fourth year of operation. The study population will consist of 234 MBBS students (students in the dental program are not eligible) distributed over four cohorts. Purposive sampling will be used. Newly registered MBBS students will be excluded from the study because their brief period in the program is not adequate to evaluate their academic performance and psychoeducational variables.

Mapping of the correlation coefficient values (over a defined range from .20 to .80) for association of resilience to academic performance with a range of power values (0.60 to 0.90; Table 3) indicates that the number of participants will be suitable for the statistical correlations performed in the study. To detect a simple correlation between resilence and academic performance, where correlation coefficient r=.20 of N observations using a 2-sided test of 5% significance level (alpha=.05) with 80% power (β=0.20), the required sample size is approximately 194.

Learning Approaches Evaluation

Our study will employ a modification of the Approaches and Study Skills Inventory for Students (ASSIST; Multimedia Appendix 1) questionnaire [33] to evaluate the predominant learning approaches of the students. This questionnaire was developed by Entwistle et al [30] to evaluate approaches to learning and has been refined and improved based on educational philosophies put forth by Martin and Saljo [34] and others [29].

The initially published ASSIST questionnaire consists of sections A, B, and C with questions rated on a Likert scale. As shown in Table 4, in the proposed research the 66 items have been reduced to 41 items (sections B and C). We modified the questionnaire to decrease the number of questions while maintaining an equal number of questions across the learning approaches. In the modified ASSIST, 4 items have been added to record the demographics of participants (age, gender, year of study in the MBBS program, and high school education). In modifying the ASSIST questionnaire, care has been taken such that overall validity of the tool is preserved. The original ASSIST questionnaire [30] has been amended instead of using an existing abridged version to make the tool as relevant as

possible to the context of the proposed research. Modifications have been introduced to avoid survey fatigue among participants; specific items not relevant to the participants have been removed. Additionally, upon piloting the questionnaire we found that the language in a few items was ambiguous, and we amended these items.

Figure 3. The 6-year undergraduate medical curriculum at Mohammed Bin Rashid University of Medicine and Health Sciences is divided into three phases. Each phase of the curriculum includes integrated courses and builds on the preceding one such that the curriculum is a spiral: the students repeat the study of a subject, each time at a higher level of difficulty and in greater depth.

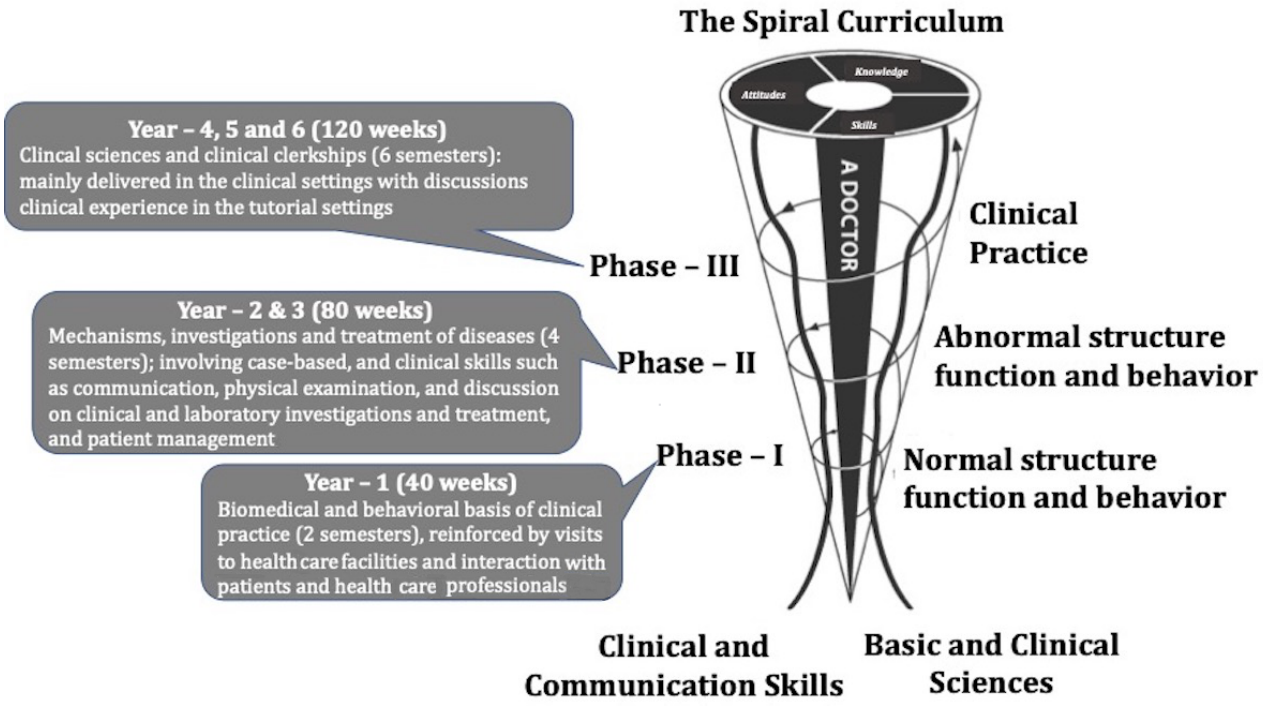


Table 3. Power calculation table.

Power of the study (1-β)	Sample correlation (*r*)						
	.20	.30	.40	.50	.60	.70	.80
0.90	259	113	62	38	25	17	12
0.80	194	85	47	29	19	13	10
0.70	153	67	37	23	16	11	8
0.60	122	54	30	19	13	10	7

Table 4. Modified Approaches and Study Skills Inventory for Students questionnaire to be implemented in this study.

Section	Content	Scale	Modifications
A	Conceptions of learning	Likert scale (1-5)	Removed a-f
B	Approaches to studying	Likert scale (1-5)	33/52 questions included (11 per learning approach)
C	Preferences for different types of courses and teaching	Likert scale (1-5)[a]	No modifications (9 total questions)
Added	Demographics	Continuous	Age, gender, year of study, high school education

[a]Last question: perceived academic performance rating (1-9).

Resilience Evaluation

The Connor-Davison [35] and Wagnild-Young [36] resilience scales were considered for our evaluation. We chose the Wagnild-Young scale (Multimedia Appendix 2) because it was developed using an oblimin rotation factor analysis (allowing correlatation) where the factor construction characterizes personal competence and acceptance of self and life [37]. The scale consists of 14 Likert-scale items grouped in five domains: self-reliance, meaning, equanimity, perseverance, and existential aloneness.

Coping Strategies Evaluation

A 13-item coping strategies questionnaire has been designed (Multimedia Appendix 3) that will assess participant cognitive, emotional, and behavioral approaches for tackling difficulties

and problems. The cognitive and emotional approaches (items 2, 3, and 4) have been adapted from the Coping Strategies Scale of Holahan and Moos [38]. Additional items focusing on emotional and cognitive approaches (items 1, 5, 6, and 8) have been adapted from Hamby et al [39]. Other items in the questionnaire are from Spitzberg et al [40].

Data Collection Procedure

Students participating in the proposed research will receive identical information, disseminated through Google Forms, similar to previous research studies conducted in medical education at MBRU [41-43]. Participants will respond to the questionnaires during the self-study time between 11 am and 1 pm (after the morning teaching sessions). Gathering and processing of the collected data will be pursued with the informed consent of the participating students, in line with the ethical and deontological principles of psychology. Collected data will be analyzed in an anonymous and group format, and the data will be stored in an encrypted database and on a password-protected solid-state drive with the research team.

We submitted the proposal to MBRU institutional review board (IRB) for which exemption has been awarded (application ID: MBRU-IRB-2019-013). Further clarification with regard to the policies and terms of reference can be obtained from the IRB.

Data Analysis

The questionnaire response files from Google Forms will be converted to a spreadsheet, and the questions for each approach will be organized into adjacent columns with the value of each response in the respective row. All collected data will be cross-verified by two investigators from the research team. The average score for each questionnaire will be generated for each student. This will be done by taking the average of all responses recorded for a certain questionnaire for a particular student.

SPSS Statistics for Windows version 23.0 (IBM Corp) will be used for all statistical analyses. Cronbach alpha will be used to check internal consistency, and explanatory factor analysis will be used specifically for the questionnaire to confirm the evidence of its validity in the literature. Outliers will be identified by using a Bonferroni outlier test (P<.05). Scores of independent variables (resilience, stress-coping strategies, and learning approaches) will be calculated for independent variables. All scores will be tested for normality by using the Shapiro-Wilk test. An inter-item correlational matrix of the dependent and independent variables to test the pairwise correlation will be formed using Pearson bivariate correlation coefficients. Regression models will be used to answer questions with type II analyses of variance in tests involving multiple predictors. Regression analyses will be checked for homogeneity of variance (Levine test), normality of residuals, and multicollinearity (variance inflation factor). Statistical significance will be set at the conventional 5% threshold (alpha=.05). Effect sizes will be estimated with 95% CIs.

Ordered logistic regression will be used to analyze the effect of individual psychoacademic variables on academic performance controlling for age, gender, and cohort to which the student belongs.

Ethical Considerations

Distributive Justice

Distributive justice in medical education in line with the concept of egalitarianism [44] dictates that all subjects in the study population are provided with just and equal opportunity to participate in the study [45]. The principal investigator is the course director/instructor for several courses across different student cohorts and therefore has regular and extensive interactions with students. Due to this interaction with students, he may develop the preconceived notion that certain students in these cohorts, because of their personality traits, should not participate in the study. As a result, these students may be inadvertently left out if the recruitment of study participants is pursued by the principal investigator. To address this, participation of students from individual cohorts will be overseen by student representatives randomly assigned from each cohort.

Beneficience

Although studies pertaining to the “July phenomenon” (rise in the morbidity and mortality of patients with the inflow of new medical trainees) [46,47] have been unfounded, they have raised concerns regarding beneficence in medical education research. Keeping in mind the key aspects of beneficence, this study includes validated questionnaires and analytical tools and methodologies that have been used in other similar studies without any untoward physiological and psychological effect on the participants. Also, recruitment of participants will involve the use of smart applications (relying less on human involvement), which will minimize harm to the participants from relatively inexperienced researchers (students overseeing recruitment, etc).

Power Differential

The power differential under the five bases of power (coercive, reward, legitimate, referent, and expert [48]) must be considered because one of the principal investigators is both the primary researcher and the course director/instructor for several courses across different student cohorts in the study. To prevent such a power differential from compelling subjects to participate in the study, recruitment and associated processes will be carried out by a faculty member from the MBRU school of dentistry, who isn’t in a power relationship with the undergraduate medical students.

Respect for Participants

One of the key aspects of the Helsinki declaration on ethical guidance on research involving human subjects requires researchers to acknowledge autonomy of study participants and protect those with diminished autonomy [49]. Therefore, data will be obtained only from consenting participants. All study participants will be required to sign a consent form.

Confidentiality

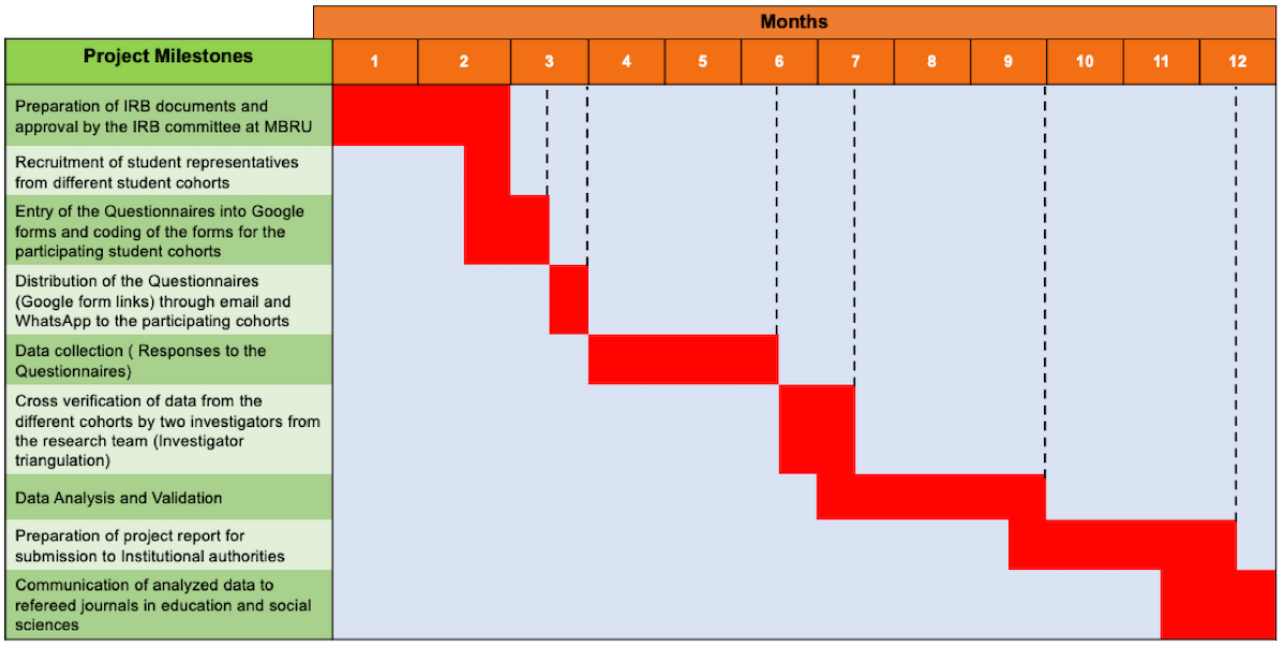
Each participant will be assigned a unique study identifier. No participant names will be collected. Participant responses will be de-identified or anonymized and reported in aggregate. A repository will be created containing participant responses, which will be encrypted and password-protected.

Results

This study is at the protocol development stage only, and as such, no results are available. The psychoeducational instruments in the form of validated questionnaires have been identified in relation to the objectives. These questionnaires have been formatted for integration into Google Forms such that they can be electronically distributed to the consenting participants.

The MBRU IRB reviewed this study and provided an exempt status (MBRU-IRB-2019-013). Further clarification and information can be obtained from the MBRU IRB at irb@mbru.ac.ae. There is no funding in place for this study and no anticipated start date. The total duration of the proposed research is 12 months. Key project milestones and timeline are shown in Figure 4.

Figure 4. Important project milestones. IRB: institutional review board; MBRU: Mohammed Bin Rashid University of Medicine and Health Sciences.



Discussion

Summary

We have presented the data from an initial study, where we have correlated student learning approach to academic performance. Data from this initial study further encouraged us to investigate academic performance of medical students in a multidimensional setting; when resilience and stress-coping strategies are also included, the study protocol for this investigation is presented in this article.

Findings from this investigation will elaborate on the need for further research regarding resilience in medical students and how resilience can be improved in this population and emphasize that the concepts of stress, burnout, resilience, and coping appear to be very much related in the context of undergraduate medical education.

Limitations

The investigated variables, resilience, learning approaches, and stress-coping strategies, are individual traits; students' learning history before they joined MBRU is unknown, so our research will not be able to address this specific aspect. Investigating this aspect would be difficult as the MBRU student pool draws from 19 different countries and 15 different high school curricula.

In addition, we cannot consider the gender variable in this study as more than 80% of our students are women, which has shown to have an effect on the investigated variables [50,51].

Conclusions

Results from the different psychoeducational instruments will institute the associative and extrapolative multidimensionality of the different variables in envisaging academic performance of medical students. To our knowledge, no study exploring the multidimensional association of learning approach, resilience, stress-coping strategies, and academic performance in undergraduate medical students has been pursued [52].

Additionally, this research will validate and expand on previous research on the importance of resilience and its association with academic stress and coping strategies in medical students [53,54]. Study results may initiate a framework for assessing psychoeducational variables while admitting students to medical school or during counseling as part of psychoeducational services.

Future studies from this research should investigate the associations of the studied psychoeducational variables with academic emotions or insufficient approaches of stress management, [55-57]. Study results can initiate strategies to integrate the studied variables in different models of medical curricula [58,59], adding to the understanding of the role of

meta-motivational and meta-affective approaches during learning in medical school [60].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Modified Approaches and Study Skills Inventory for Students [32] questionnaire.
[PDF File (Adobe PDF File)180 KB - resprot_v8i9e14677_app1.pdf]

Multimedia Appendix 2
The 25-item Resilience Scale of Wagnild and Young [35].
[PDF File (Adobe PDF File)172 KB - resprot_v8i9e14677_app2.pdf]

Multimedia Appendix 3
The 13-item Coping Scale.
[PDF File (Adobe PDF File)181 KB - resprot_v8i9e14677_app3.pdf]

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Abbreviations

ASSIST: Approaches and Study Skills Inventory for Students
CLSPS: competence of learning, studying, and performing under stress
IRB: institutional review board
MBBS: Bachelor of Medicine, Bachelor of Surgery
MBRU: Mohammed Bin Rashid University of Medicine and Health Sciences

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Protocol

Digital Tracking of Rheumatoid Arthritis Longitudinally (DIGITAL) Using Biosensor and Patient-Reported Outcome Data: Protocol for a Real-World Study

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Abstract

Background: Rheumatoid arthritis (RA) is a condition with symptoms that vary over time. The typical 3- to 6-month interval between physician visits may lead to patients failing to recall or underreporting symptoms experienced during the interim. Wearable digital technology enables the regular passive collection of patients' biometric and activity data. If it is shown to be strongly related to data captured by patient-reported outcome (PRO) measures, information collected passively from wearable digital technology could serve as an objective proxy or be complementary to patients' subjective experience of RA symptoms.

Objective: The goal of this study is to characterize the extent to which digital measures collected from a consumer-grade smartwatch agree with measures of RA disease activity and other PROs collected via a smartphone app.

Methods: This observational study will last 6 months for each participant. We aim to recruit 250 members of the ArthritisPower registry with an RA diagnosis who will receive a smartwatch to wear for the period of the study. From the ArthritisPower mobile app on their own smartphone device, participants will be prompted to answer daily and weekly electronic PRO (ePRO) measures for the first 3 months.

Results: The study was launched in December 2018 and will require up to 18 months to complete. Study results are expected to be published by the end of 2021.

Conclusions: The completion of this study will provide important data regarding the following: (1) the relationship between passively collected digital measures related to activity, heart rate, and sleep collected from a smartwatch with ePROs related to pain, fatigue, physical function, and RA flare entered via smartphone app; (2) determine predictors of adherence with smartwatch and smartphone app technology; and (3) assess the effect of study-specific reminders on adherence with the smartwatch.

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KEYWORDS

real world evidence; real world data; patients; rheumatoid arthritis; patient-reported outcomes; patient-generated health data; mobile technology; wearable digital technology

Introduction

As the selection and availability of consumer-grade digital technology to measure biometric and activity outcomes have increased dramatically in recent years, their use in clinical and observational studies have also grown. At a minimum, biosensor technology typically measures heartbeat, activity, and sleep, yet these tools have been used primarily in research in disease states with core symptoms that are clearly directly measurable using such technology (eg, Parkinson's disease) [1]. An individual's level of activity and sleep quality can be affected by many other conditions, such as migraine, diabetes, systemic lupus erythematosus, atopic dermatitis, obesity, and arthritis. The ability to observe symptom changes in real time (particularly in response to pharmacotherapy and behavior changes) using mobile biosensor technology has the potential to significantly enhance treatment of chronic disease by enabling more rapid and focused deployment of interventions.

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis and often results in joint damage that, without adequate treatment over time, may lead to disability, pain, limitations in physical function, and other impairments important to patients [2]. Treating clinicians typically see RA patients at 3- to 6-month intervals. Assessments at clinician visits are necessary, but not enough, to understand the full spectrum of a patient's clinical state, progression, and the waxing and waning nature of their symptoms. The true severity of pain and flares experienced between visits may not be captured at office visits due to recall bias. To understand the extent of RA disease activity, especially attributes related to pain and stiffness, it is essential to collect patient-reported outcome (PRO) measures in a low-burden, continuous frequency instead of an episodic frequency. PRO measures may include health-related quality of life, physical function, fatigue, sleep, mental health status, work productivity and work activity impairment [3].

PRO measures direct patients to report on their experience and therefore supply unique data for the management of RA. Because PROs are reported directly by patients on paper or electronic questionnaires, they reflect how a patient feels and functions in relation to RA and its therapy [4,5]. Although PRO measures necessitate patient attention and effort, they are also useful for understanding a patient's subjective experiences. They can help to facilitate clinician-patient communication and shared decision-making to improve the quality of patients' care, and they can help to identify both common and divergent perceptions of disease activity and treatment effectiveness between clinician and patient. While the advent of smartphone technology has enabled convenient and remote capturing of electronic PRO measures (ePROs) between in-person clinician visits [6,7], a patient must still recall their symptoms over a day- or week-long period. In the quest for additional patient-generated data to complement patients' reported experiences of physical function, pain, sleep, fatigue, and so on, biometric sensors may play an important role in providing continuously captured objective data (ie, activity, heart rate and sleep hours).

To date, there are few published studies investigating the extent to which biometric data correspond with RA patients' subjective reports of their symptoms and disease activity. Performance outcome measures (eg, gait, distance traveled, and acceleration) collected passively using smartphone applications have been found to be associated with RA symptoms in studies with small samples ranging from 20-80 participants [8,9]. A recent proof of concept, human factors study explored the experience of 15 subjects who wore an activity tracker daily over 1 week and completed ePRO questions about stiffness, sleep quality, and joint pain in the morning and evening. The investigators reported that initial analyses showed modest correlation between the duration of morning stiffness reported in the ePRO and the level of morning activity tracked by the activity tracker. These investigators are planning a larger trial in a clinical setting with RA subjects receiving medication [10].

In a study of 446 participants, of whom 292 were RA patients, data from daily passive digital measures (ie, Global Positioning System–tracked mobility, mobility radius number, and duration of calls and texts) were collected and associated with PRO measure data (ie, daily pain, patient global health assessment, weekly Health Assessment Questionnaire-II [HAQ-II] [11] and Patient Activity Scale-II [PAS-II] [12]). Text length was most strongly and inversely associated with PROs, including pain, and mobility measures were significantly associated with global assessment, HAQ-II, and PAS-II, but not pain [13]. The Patient Rheumatoid Arthritis Data from the Real World (PARADE) study, launched in 2016, collected ePROs and both active and passive digital data through a smartphone-customized ResearchKit application to measure morning stiffness and fatigue [14,15], but it had disappointing levels of patient engagement. Specifically, of 399 recruited participants, less than half (162; 40.6%) completed one or more study assessments at week 2, and only 45 (11%) remained active in the study by 12 weeks [15,16].

Our exploratory study will expand on these prior studies and examine a larger RA population, incorporating digital measures from a Fitbit Versa smartwatch (chosen based on the type of biometric data captured, water resistance and cost) to assess the value of passively collected digital measures as proxies for RA disease activity and other domains of health that may be affected by RA, as reflected in ePROs. Our study differs from PARADE in the use of smartwatch technology and in the manner of participant recruitment. The PARADE study developed a set of wrist activities to measure range of motion [15], but the activity measurement in our study will be passively collected with the smartwatch. Although less sensitive measures are available via the smartwatch, the ability to collect some measure of activity without requiring participant input is an advantage. In addition, PARADE used a broader approach to identify participants in the United States via targeted digital marketing on social media platforms including Facebook, Twitter, and HealthUnlocked. They also made study information available to Facebook users who followed CreakyJoints. In contrast, our study will enroll patients exclusively from members of ArthritisPower, a CreakyJoints-affiliated research registry in the United States. We believe working within an existing population that is already oriented to sharing ePROs will result

in greater participant retention. Unlike PARADE, there will be no randomization into groups based on data sharing with the participant during our study, as all participants will be able to view the same amount of their own data throughout. Additionally, PARADE was conducted entirely via app, with no financial incentives and human interaction. In our study, participants will receive compensation based on specific milestones, and members of the research team will monitor their data in real time and, under certain criteria, contact participants when missing data patterns suggest nonadherence to protocol or difficulty in using the technology. Real-time data monitoring offers the opportunity to clarify protocol procedures directly with individual participants.

Specifically, this study seeks to evaluate the potential relationship between passively collected digital measures related to activity, heart rate, and sleep, collected from a smartwatch, with ePROs related to pain, fatigue, physical function, RA disease activity and flare in participants with RA over the 3-month main study period. In the lead-out period, participants' use of smartwatch technology will continue to be observed for another 3 months.

The secondary objectives of this study are to: (1) examine the variability of measurement of data derived from digital measures; (2) assess the test-retest reliability and both the convergent and discriminant validity of the digital measures; and (3) determine predictors of adherence with the technology, both with the app and smartwatch.

Exploratory objectives of this study include: (1) evaluating the effect of reminders on adherence with smartwatch use by comparing engagement during the main study period (months 1-3) and lead-out period (months 4-6); and (2) identifying the scientific and operational benefits as well as the challenges confronted in characterizing the burden of illness in RA with digital measures to inform future, digital, real-world evidence studies.

Methods

Research Design

Overview

This is an ancillary study conducted within the ArthritisPower registry infrastructure. ArthritisPower was jointly developed by the nonprofit Global Healthy Living Foundation (GHLF), its associated CreakyJoints arthritis patient community, and rheumatology researchers at the University of Alabama at Birmingham (UAB) [17,18], and funded through a Patient-Centered Outcomes Research Institute Award (Contract Number PPRN-1306-04811). ArthritisPower currently has over 18,000 consenting participants, about half of whom report a physician diagnosis of RA. As part of their membership in the ArthritisPower registry, participants have downloaded the ArthritisPower app used for ePRO measures collection. This ancillary study, sponsored by Eli Lilly and Company, will collect ePRO measures from RA participants via a customized, study-specific user flow within the ArthritisPower app while measures of activity, heart rate, and sleep will be collected passively using the smartwatch.

The DIGITAL Tracking of rheumatoid Arthritis Longitudinally (DIGITAL) study includes a 10- to 14-day lead-in period, 12-week main study period, and 12-week lead-out period (Figure 1).

Lead-In Period

Prior to receiving their smartwatch, invited participants will successfully complete a 14-day lead-in period during which they are required to meet the following inclusion criteria: (1) complete two daily ePRO measures, specifically the single-item Pain and Fatigue numeric rating scales (NRS), on at least 10 of the 14 days; and (2) complete two weekly core sets of ePRO measures (Table 1), over the 14-day period. Those who do not meet these requirements will be offered a single opportunity to repeat the lead-in period and subsequently qualify for the remainder of the DIGITAL study. This initial phase will serve to acclimate participants to regular data collection and provide some assurance that they are willing and able to take part in and complete study requirements over the 3-month main study period.

Figure 1. Overall study design. *Active data collection of 2 daily questionnaires begins 2-4 weeks prior to receipt of smartwatch and continues throughout the study. Other electronic patient-reported outcomes measures will be collected weekly. Digital data from the smartwatch will be collected passively.

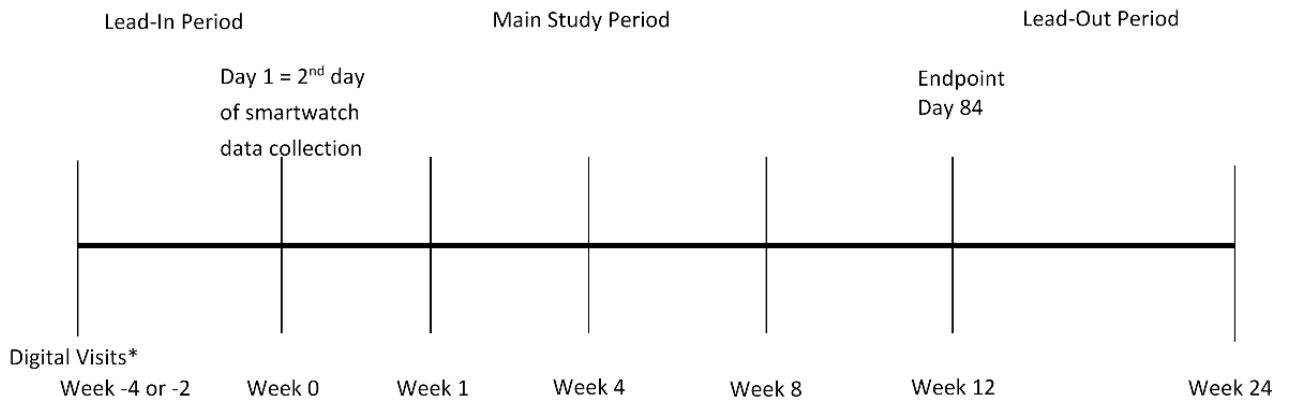


Table 1. Variables and measures.

Categories and variables (frequency/source)	Definition
Demographic and baseline clinical characteristics (once at registration/ArthritisPower)	
Age	• Date of birth
Gender	• Male or female
Race	• American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, Caucasian, multiple race, RTA[a]
Hispanic ethnicity	• No, unknown, yes
Zip code	• 5-digit US postal code
Condition(s)	• Rheumatoid arthritis
Years since RA[b] diagnosis	—[c]
Rheumatologist name	• National Provider Identifier lookup by city, state
Height	—
Weight	—
Current medications, supplements, vitamins, over the counter, and other nonprescription remedies	• DMARD[d] medication class for all medications taken for the treatment of RA. This attribute serves as confirmation of self-reported RA as well as a baseline covariate.
Telephone number (cellular)	—
Preference for email versus text notifications and reminders	—
Typical work schedule	—
Typical sleep schedule	—
ePRO[e] measures	
Pain, single-item NRS[f] (daily/ArthritisPower)	• 0 (no pain) - 10 (pain as bad as it could be) at 0.5 intervals
Fatigue, single-item NRS (daily/ArthritisPower)	• 0 (no fatigue) - 10 (worst possible fatigue) at 0.5 intervals
PROMIS-CAT[g] Fatigue (weekly/ArthritisPower)	• 0-100 t-score; 0 - <55 (within normal limits), 55 - <60 (mild), 60 - <70 (moderate), ≥70 (severe)
PROMIS-CAT Pain Interference (weekly/ArthritisPower)	• 0-100 t-score; 0 - <55 (within normal limits), 55 - <60 (mild), 60 - <70 (moderate), ≥70 (severe)
PROMIS-CAT Physical Function (weekly/ArthritisPower)	• 0-100 t-score; ≥55 (within normal limits), 40 - <55 (mild), 30 - <40 (moderate), <30 (severe)
PROMIS-CAT Satisfaction with Participation in Discretionary Social Activities (weekly/ArthritisPower)	• 0-100 t-score; ≥55 (within normal limits), 40 - <55 (mild), 30 - <40 (moderate), <30 (severe)
PROMIS-CAT Sleep Disturbance (weekly/ArthritisPower)	• 0-100 t-score; 0 - <55 (within normal limits), 55 - <60 (mild), 60 - <70 (moderate), ≥70 (severe)
OMERACT[h] RA Flare (weekly/ArthritisPower)	• 0 (low) - 50 (high)
Godin Leisure-Time Physical Activity Questionnaire (weekly/ArthritisPower)	• 0-23 (insufficiently active), ≥24 (active)
Adherence to ePRO measure completion (daily or weekly/ArthritisPower)	• Ratio of completed ePROs to number of required ePROs prior to discontinuation or end of study period

Categories and variables (frequency/source)	Definition
Persistence with ePRO measure completion (daily or weekly/ArthritisPower)	• Days until first incomplete or missing ePRO within study period
Passively collected biosensor data (continuous [if smartwatch is synced every <5 days]/Fitabase)	
Activity	• Steps (minute, hour, day) • Activity intensity (minute, hour, day) • Distance (day) - units = miles • Energy expenditure (minute, hour, day) • Metabolic Equivalents (minute)
Activity-derived variables	• Time walking per day (minutes) • Time in activity intensity categories per day (minutes) • Active time (minutes) • Aerobic time (minutes)
Heart rate	• Beats per minute (minute, day)
Heart rate–derived variables	• Time in heart rate zone of interest based on exercise charts
Sleep	• Time sleeping in last 24 hours (minute, day)
Sleep-derived variables	• Time in light, deep, and REM[i] sleep and time to sleep onset, time awake and other derived variables (day)
Adherence to wearing and syncing smartwatch	• Ratio of days with smartwatch data to number of days during study period prior to discontinuation or end of study period
Persistence with wearing and syncing smartwatch	• Days until first day without any smartwatch data in Fitabase

[a]RTA: refuse to answer.

[b]RA: rheumatoid arthritis.

[c]Not applicable.

[d]DMARD: Disease-Modifying Antirheumatic Drug.

[e]ePRO: electronic patient-reported outcome.

[f]NRS: numeric rating scale.

[g]PROMIS-CAT: Patient-reported outcome measurement information system-computer adaptive testing.

[h]OMERACT: Outcome Measures in Rheumatology.

[i]REM: rapid eye movement.

Main Study Period

Upon successful completion of the lead-in period, participants will receive a Participant Kit that will contain a smartwatch, on-boarding and training materials, and instructions to access study resources such as frequently asked questions, training videos, and research team contact information. Participants will receive reminders as smartphone lock-screen notifications and as emails to sync their smartwatch data and complete their ePROs during the subsequent 84 days. To avoid sending extraneous notifications to those participants who are consistent in smartwatch data download, syncing, and ePRO completion, ArthritisPower will use the daily Fitbit and ePRO data to provide targeted text, email, and phone follow-up reminders, as well as support to participants whose data are missing for one or more days.

Lead-Out Period

Following the main study period is a three-month lead-out period, during which no reminders to sync the smartwatch will be sent and no ePRO collection will be prompted beyond normal monthly reminder emails that are sent to all participants in the ArthritisPower registry. The purpose of the lead-out period is to assess the effect of reminders on the main study, observe the attrition in smartwatch use, and assess any changes in smartwatch measures when not actively solicited.

Pilot

The study will begin by enrolling a pilot cohort of 10-20 participants who will provide feedback about their experience during the lead-in period and initial setup for the main study period. Participant feedback during the pilot will allow for operational adjustments to be made prior to the larger study start. Participants will provide feedback via emailed questionnaires and phone calls on various logistical aspects, including receiving and completing ePRO measures via the smartphone app, getting a shipped package (Participant Kit) containing the smartwatch, and setting up the smartwatch. This feedback will be used to adjust the smartwatch provisioning process as needed. Any major proposed adjustments would be submitted to the Institutional Review Board for review and approval prior to implementation.

Study Population

GHLF will send eligible members of the ArthritisPower research registry an invitation to participate in this study. Participants within the ArthritisPower registry are eligible to join this study if they provide informed consent and meet each of the inclusion criteria listed in Textbox 1.

Compensation

Participants who complete all activities for the first 4 weeks of the main study period will receive a US $25 gift card, and those who complete all activities for all 12 weeks of the main study period will receive an additional US $50 gift card.

Data Collection

Participants who successfully complete the 14-day lead-in period will be issued a smartwatch that will be used to collect digital measures of activity, heart rate, and sleep. The participants are not required to return their smartwatch at the end of the study. Day 0 of the study is the date that the first smartwatch data will be observed from the participant. The following day is Day 1 for analysis purposes, as it will constitute a full 24-hour period of data collection.

Variables and Measures

Table 1 presents the study variables and their operational definitions. The t-score used to measure the Patient-reported outcome measurement information system-computer adaptive testing (PROMIS-CAT) is a standardized score based on the overall (healthy) US population where 50 is the average (mean), which allows us to see how much above or below (ie, number of standard deviations) a person's PROMIS-CAT ePRO deviates from the mean.

Data Workflow

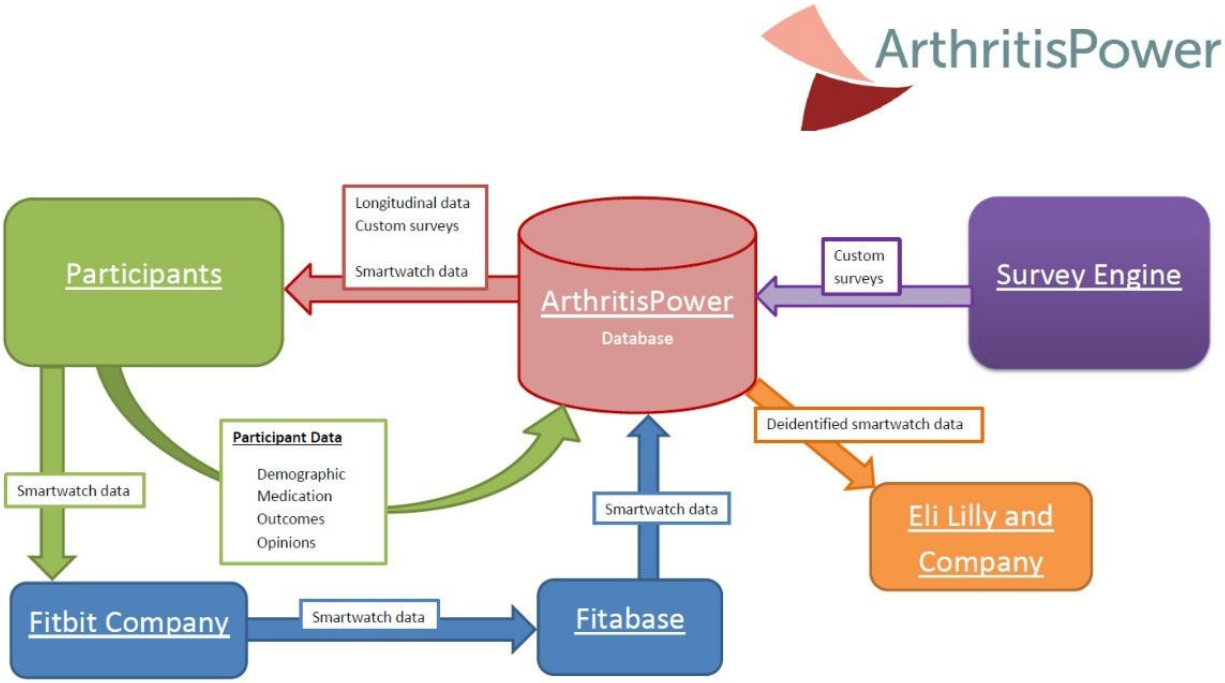
GHLF will send eligible members of the ArthritisPower research registry an invitation to participate in this study. Once enrolled, participants will provide daily and weekly survey data to be stored in the ArthritisPower database. During the main study period, participants will be equipped with preconfigured Fitbit accounts linked by GHLF to the Fitabase platform. The Fitabase platform will stream the participants' activity metrics directly from the Fitbit cloud. This will allow the research team at GHLF and UAB to monitor participant sync and charge activity and send participation reminders. Accessing Fitabase via an exposed application programming interface enables automation of this process.

Identifying information will be collected separately from survey responses and digital measures of activity, heart rate, and sleep to protect participant privacy and maintain a deidentified data set. All identifying information collected will be handled by internal ArthritisPower research staff, as per guidelines specified in ArthritisPower protocol. All data collected through this study will be analyzed, stored, and collected by ArthritisPower staff at GHLF and UAB. Individual identities will only be used by ArthritisPower staff at GHLF and UAB to send smartwatches and follow up with participants to troubleshoot problems with data collection or syncing. Any results will be reported in a deidentified or aggregated form. All information will be stored and protected in password protected files and can only be accessed by the ArthritisPower research team. The only participant-level data that will be shared with Eli Lilly and Company is the deidentified smartwatch data to enable greater understanding of passively collected smartwatch data. It will not be possible for the research team at Eli Lilly and Company to contact participants for this study. Any identifying information collected will not be included in any notes or report documents used by the team. Data flow throughout the study is outlined in Figure 2.

Textbox 1. Inclusion criteria for the DIGITAL study.

- Age 19 or older
- US resident
- Self-reported diagnosis of rheumatoid arthritis
- Registered a valid email address with ArthritisPower
- Currently being seen by a US rheumatologist
- Currently taking at least one conventional synthetic or targeted disease-modifying antirheumatic drug for rheumatoid arthritis, but not baricitinib
- Own a smartphone (iPhone 4S and later or Android 4.3 and later) to which they have downloaded the ArthritisPower app
- Are willing to contribute daily and weekly ePROs for up to 98 days, and health activity tracker data for at least 84 days
- Are willing to wear the smartwatch while sleeping
- Will not be out of internet access (Wi-Fi or mobile data) for 4 or more consecutive days during the study
- Successfully complete the lead-in period
- Are willing to be contacted by e-mail or phone by a study coordinator if they fail to adhere to the study protocol

Figure 2. Study data workflow.



Analyses

Primary Analyses: Agreement Between ePRO and Passively Collected Digital Measures

The primary objective of this study is to quantify the agreement between passively collected digital measures (eg, activity) and ePRO data (eg, pain NRS scores). Descriptive statistics will summarize the demographics and baseline characteristics for all enrolled participants. The primary analysis will be a descriptive summary of the correlation between passively collected biosensor data and ePRO data. See Table 1 for a list of the ePRO and passively collected digital measures. For ePROs assessed weekly, multiple summary measures of the passive measures will be created over the corresponding weekly timeframe. Summaries to be explored include the average over the time period, trends, most recent, minimum, maximum, variation, and transformations in the data. Correlations between the ePRO and passive measures will be quantified using both a simple correlation matrix for each week as well as using repeated measures models over the entire study. Repeated measures models will be implemented using each ePRO as the outcome measure, with time (eg, week as a classification factor), baseline measures, and the various passive measures as potential factors in the model. The starting model will be a simple main effects model, and then a penalized regression model will also be used to optimize model selection, including the potential for 2-way interactions (including with time). This will allow for assessment of changes in correlations over time adjusted for participant level covariates.

For digital measures obtained daily, a repeated measures model will assess the association between the ePRO (outcome) and passive measures over time (with day as the time period of assessment rather than week). Daily ePRO data may lag by a day if it is observed that most participants are responding in the morning. Due to the large number of days in the study, time will be considered a numeric variable in this model.

Secondary Analyses

Test-retest reliability will be assessed by examining the correlations between each derived digital measure during time periods when observed values of the related ePROs are stable. This includes, for example, assessing the intraparticipant correlations between weekly averaged daily step counts (or associated derived variables) on weeks when participants report the same level of activity as assessed using the Godin Leisure Time Physical Activity Questionnaire [19].

Random forests, gradient boosting, and penalized regression models incorporating cross-validation will be built for detection and prediction of ePRO defined events (eg, flare, adherence, score changes). Baseline and time-varying factors (ie, ePRO, digital measures, and changes in previous time periods) will be included as potential factors in the analyses. Operating characteristics of models will be compared.

Using the Outcome Measures in Rheumatology (OMERACT) flare PRO [20], a question was added after Q7 (“Are you having a flare now?), “If yes, how long ago did it start?” Possible responses included, “I’m not having a flare at this time, Today, Yesterday, 2 days ago, 3 days ago, 4 days ago, 5 days ago, 6 days ago, 7 or more days ago,” so that this study could define the onset date of any RA flare. Descriptive statistics will summarize the trends in the daily ePRO and passive data over the last 3 days prior to the onset of the flare. To assess whether digital measures can accurately classify participants as having an RA flare or not, Classification and Regression Trees and penalized regression incorporating cross-validation will be used.

Interim and Subgroup Analyses

The interim analysis will be conducted after the initial pilot cohort have completed 4 weeks of the study.

Sample Size and Statistical Methods

We aim to recruit 250 participants who have successfully completed the lead-in period and received the smartwatch to wear for the duration of their participation in the main study and lead-out periods. Assuming at least 75% of the participants complete the majority of the measures, a sample size of 250 will provide at least 80% power to detect correlations between passively collected data via the smartwatch and the actively collected data from ePRO instruments of at least 0.2 and over 90% power to detect correlations of at least 0.3 at any given time point. The analyses will not include any adjustment for multiplicity.

Results

A user flow was designed, developed, and tested for the lead-in and main study periods of the project. Screen shots displaying the user flow for the lead-in period are shown in Figure 3 and for the main study period in Figure 4. The study was launched in December 2018 with pilot participants. As of February 2019, 17 pilot participants have enrolled in the study, have completed the lead-in period, and have received a smartwatch and begun syncing their data as part of the main study period.

Invitations were sent to 70 eligible ArthritisPower participants, with a total of 17 participants enrolling in the pilot of the DIGITAL Study. Once they completed the lead-in period and successfully started the main study period, pilot participants provided feedback via email, online questionnaire, and phone calls. The research team also examined the ePRO and smartwatch data that had been collected from pilot participants to flag preliminary issues with participant adherence to protocol procedures and missing data. Three issues emerged that were addressed via modification to the operational plan and the app software (underlying user flow for this study).

First, participants appreciated getting daily reminders during the lead-in period and asked that these daily reminders continue throughout the main study period. Second, participants were confused about the difference between their ePRO measures for the week as part of the DIGITAL Study and the regular weekly ePRO measures completed within the standard ArthritisPower registry. This made it difficult for participants to distinguish whether they had completed their DIGITAL Study tasks for the day or week. As a result, we changed the ArthritisPower app user experience for those in the DIGITAL Study so that while ArthritisPower participants are taking part in the DIGITAL Study, their regular weekly ePROs in ArthritisPower will be disabled to avoid confusion and duplication of effort. Third, smartwatch data syncing presented some challenges for participants, with at least one participant in the pilot cohort believing they were syncing data correctly even though data were not appearing to the research team as expected. After troubleshooting, we discovered that the participant had logged in to a prior, personal Fitbit account, which meant data were not captured for analysis in the study during that period of their smartwatch use. Additionally, a few pilot participants said they found the smartwatch band to be uncomfortable and would take it off, sometimes forgetting to put it back on.

Figure 3. Lead-in period screen shots: a) Participant is presented with introductory screen, reminded of lead-in requirements to be eligible for the main study, and prompted to continue to assessments; b) Participant completes assessments, including daily single-item Fatigue measure; c) Upon completion of assessment queue, participant is reminded of remaining number of sets of assessments to be eligible for the main study.

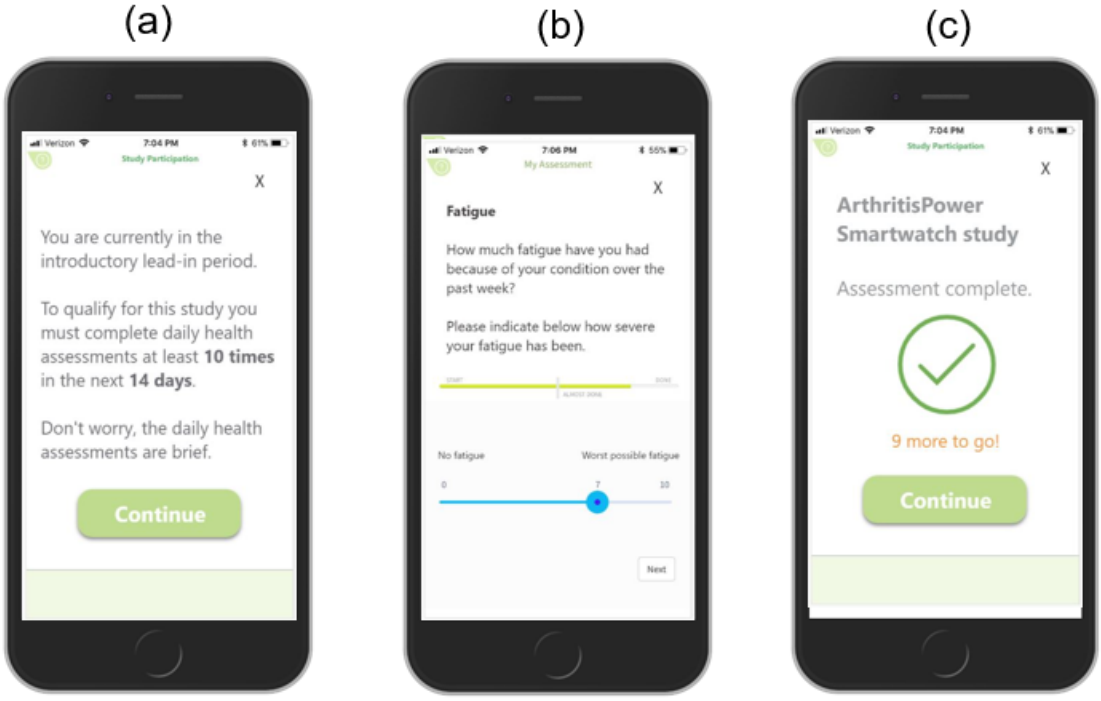
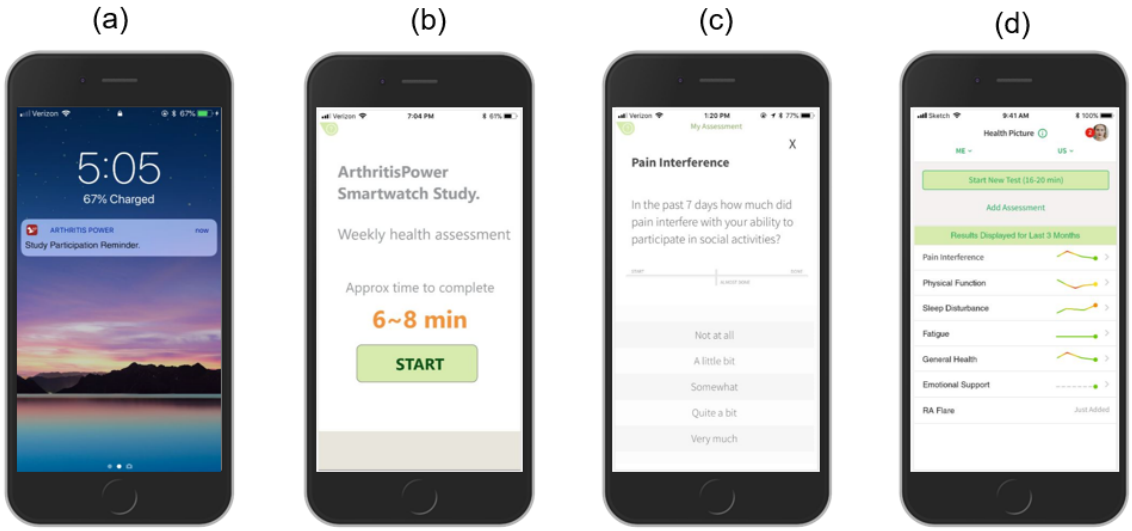


Figure 4. Main study period screen shots: a) Participant receives email and smartphone lock screen notification with reminder to complete daily and weekly assessments; b) Participant is informed of approximate time required to complete daily or weekly assessments so they can start when ready; c) Participant progresses through daily and weekly assessments, including Pain Interference; d) Upon completion of weekly assessment queue, participant sees a Health Picture summary of personal assessment scores.



We had planned several steps to minimize the technical trouble participants might encounter in syncing their smartwatch data and to enable the research team to quickly identify when smartwatch data was not being provided from a participant. First, in the Participant Kit that included the smartwatch, we provided simple set-up instructions on a "Start Here" 8.5"x11" card that included the Fitbit app download, and we included login information with a login email address and password that was unique to each participant. Since we knew in advance the participant's login information, we could immediately see who was successfully syncing as soon as they set up their smartwatch. Second, in the ArthritisPower app unique user flow for the DIGITAL study, we prompted participants to let us know when they received their Participant Kit so they could be automatically directed to download the Fitbit app. This is scheduled to occur in the app after the lead-in period to inform the research team of the exact date a participant had taken the necessary steps to set up and sync their smartwatch. Finally, to minimize the risk of perpetual missing data from syncing or incomplete ePROs, we created a partially automated case management structure to rapidly identify participants whose data indicated the need for more intensive follow-up intervention, including calls from staff. To address watch band discomfort, the research team will now make alternative bands available to participants on a case-by-case basis when flagged during case management interactions. Importantly, we noted in the pilot cohort smartwatch data that if a participant removed their smartwatch, they did so either for a short period of time (eg, to shower) and put it back on fairly quickly, or for a long time (eg, to charge). As a result, for this study we agreed that at least one minute of activity or data in a given hour would indicate that the participant's data could be used for analysis.

The DIGITAL study informed consent and study communications with participants were modified to reflect any changes to the initial operational plan following pilot cohort feedback. This exercise gave us greater confidence in participant data collected beyond the pilot cohort. It is expected that all study participants will have completed the main study period by early 2020 with results published in 2021.

Discussion

The primary objective of this study is to evaluate the relationship between passively collected digital measures related to activity, heart rate, and sleep, collected from a smartwatch, with ePROs related to pain, fatigue, physical function, RA disease activity, and flare among people living with RA over 3 months. Since passively collected data, such as step counts and heart rate, are measured in a more continuous and objective manner than ePROs, there are implications for both research and patient care depending on the strength of the correlation between these two types of data.

For research, remote data collection of trial participants could minimize participant burden and save time and money required for clinical trials due to less frequent clinical visits and fewer staff hours. Among patients, both activity trackers and remote collection of ePROs mitigate recall bias and offer the opportunity for more comprehensive data collection. Our findings may help inform future studies by identifying when ePRO data are necessary to supplement passive data and when they are not. Collecting data during the interim period between clinician visits is important for patients with RA because each day can be different, so tracking variability in how the disease behaves day-to-day may help better assess disease activity. If ultimately accepted by regulators, this could lead to greater precision and thus smaller clinical trials, resulting in more rapid approval of medications for the marketplace. Moreover, this information facilitates a quicker and more continuous stream of real-world data being generated for comparative effectiveness research. As such, the type of approach represented in this protocol might be integrated into a complete, patient-centric digital health solution and bundled with a medication prescription, a so-called Beyond the Pill approach [21]. As a result, patients and clinicians may benefit from new information

about therapies that are equally or more effective using data collected outside of a typical clinical setting. It could, for example, inform management of RA patients on combination therapy who are doing well (eg, in remission) and might consider discontinuing use of a drug without negatively affecting disease activity and symptoms.

Other possible benefits for patient care include the potential to identify treatment effectiveness between office visits, detect arthritis flare, accelerate clinical reevaluation, and speed up treatment modification when disease activity appears to be active, but this fluctuates frequently with intermittent flares. Monitoring patients remotely between visits in a manner that minimizes patient burden and does not require that a patient do more than wear a device could dramatically increase the amount and availability of data to inform specialists and primary care physicians about patients in their care, as well as contribute important information to assist with quality reporting and improvement [22].

There are several challenges related to passive data collection and the comparative analyses conducted with such data that we sought to address with this protocol. Wearables are appealing in terms of data collection over more hours each day, yet device selection is critical for patient adherence. Participants are more likely to be adherent for a longer duration when wearing commercial-grade devices that may lack the precision of fit for purpose research-grade devices. Passive data are available only when study participants remember to wear their device and correctly sync or download their data on a regular basis. To minimize the risk of missing data, we created a partially automated case management structure to rapidly identify participants requiring more intensive follow-up intervention. Passive data collection in the context of virtual studies such as this one requires more up-front investment of time to develop patient-centric onboarding materials and digital interfaces, operational plans for regular data review to identify issues with collection, and staffing to address questions that arise during technology onboarding and use.

Second, acceptable wear patterns must be established in advance to determine which downloaded device data actually indicate a participant's use of the device for analytical purposes. The unit of measurement and associated time boundaries for analysis must be defined and described in the statistical analysis plans or programming requirements. For this study, we agreed that at least one minute of activity or data in a given hour would indicate that the participant's data could be used for analysis. Comparison of continuous, minute-level data with data received only once daily or weekly makes the time cut-offs even more important and influential on results when lining up the data. Although tempting to seek strong correlations and good fitting models, there is substantial value in uncovering differences between passive real-time data and periodic ePRO measures. The increased variability and periodic divergence may lead to lower correlations, but they are also the reason multimodal assessment and an associated understanding of the different data streams is critical.

Finally, from a generalizability perspective, passive data collection requires participants that have a level of comfort with technology. The PARADE study observed that participants tended to have more years of formal education and be younger than the nationally representative cohort used for comparison [15]. Thus, research populations employing such technology represent a subsample that may not adequately represent important segments of patients with the disease in question.

The findings of this study may ultimately provide guidance for patient-focused drug development among regulators, specifically with the US Food and Drug Administration. A clearer characterization of how different types of patient-generated data describe the patient experience in a complementary fashion may help determine how and where to incorporate each data type into the regulatory decision-making process. Both ePRO measures and biometrics shed light on the patient experience, but on different aspects. Biometrics can continuously capture data like activity, heart rate, and sleep quality in a way that ePROs cannot, but there are aspects of activity, sleep, and other physical, mental, emotional, and social health domains related to biometric readings that biometrics alone are insufficient to understand. Daily and weekly ePRO measures like pain and fatigue that are being examined in this study are ideal for exploring the complementary nature of patient-reported and biometric data.

Conflicts of Interest

WBN, JRC, DC, SV, and KG were involved in the development of the ArthritisPower app. WBN, JRC, SV, and CLK participate in ArthritisPower registry governance. SKN, JLP, ABC, CLK, DEF, and VSH are employees and stockholders of Eli Lilly and Company. JRC has received grant, research support, and consulting fees from Eli Lilly and Company. The remaining authors declare no conflicts of interest.

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Abbreviations

ePRO: electronic patient-reported outcome
GHLF: Global Healthy Living Foundation
HAQ-II: Health Assessment Questionnaire-II

NRS: numeric rating scales
OMERACT: Outcome Measures in Rheumatology
PARADE: Patient Rheumatoid Arthritis Data From the Real World Study
PAS-II: Patient Activity Scale-II
PRO: patient-reported outcome
PROMIS-CAT: patient-reported outcome measurement information system-computer adaptive testing
RA: rheumatoid arthritis
UAB: University of Alabama at Birmingham

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Protocol

Wearable Digital Sensors to Identify Risks of Postpartum Depression and Personalize Psychological Treatment for Adolescent Mothers: Protocol for a Mixed Methods Exploratory Study in Rural Nepal

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Abstract

Background: There is a high prevalence of untreated postpartum depression among adolescent mothers with the greatest gap in services in low- and middle-income countries. Recent studies have demonstrated the potential of nonspecialists to provide mental health services for postpartum depression in these low-resource settings. However, there is inconsistency in short-term and long-term benefits from the interventions. Passive sensing data generated from wearable digital devices can be used to more accurately distinguish which mothers will benefit from psychological services. In addition, wearable digital sensors can be used to passively collect data to personalize care for mothers. Therefore, wearable passive sensing technology has the potential to improve outcomes from psychological treatments for postpartum depression.

Objective: This study will explore the use of wearable digital sensors for two objectives: First, we will pilot test using wearable sensors to generate passive sensing data that distinguish adolescent mothers with depression from those without depression. Second, we will explore how nonspecialists can integrate data from passive sensing technologies to better personalize psychological treatment.

Methods: This study will be conducted in rural Nepal with participatory involvement of adolescent mothers and health care stakeholders through a community advisory board. The first study objective will be addressed by comparing behavioral patterns of adolescent mothers without depression (n=20) and with depression (n=20). The behavioral patterns will be generated by

wearable digital devices collecting data in 4 domains: (1) the physical activity of mothers using accelerometer data on mobile phones, (2) the geographic range and routine of mothers using GPS (Global Positioning System) data collected from mobile phones, (3) the time and routine of adolescent mothers with their infants using proximity data collected from Bluetooth beacons, and (4) the verbal stimulation and auditory environment for mothers and infants using episodic audio recordings on mobile phones. For the second objective, the same 4 domains of data will be collected and shared with nonspecialists who are delivering an evidence-based behavioral activation intervention to the depressed adolescent mothers. Over 5 weeks of the intervention, we will document how passive sensing data are used by nonspecialists to personalize the intervention. In addition, qualitative data on feasibility and acceptability of passive data collection will be collected for both objectives.

Results: To date, a community advisory board comprising young women and health workers engaged with adolescent mothers has been established. The study is open for recruitment, and data collection is anticipated to be completed in November 2019.

Conclusions: Integration of passive sensing data in public health and clinical programs for mothers at risk of perinatal mental health problems has the potential to more accurately identify who will benefit from services and increase the effectiveness by personalizing psychological interventions.

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KEYWORDS

developing countries; feasibility studies; mobile health; mother-child interaction; postpartum depression; psychotherapy

Introduction

Background

There is a global crisis of untreated depression [1]. Lack of treatment for postpartum depression is especially harmful because of long-term consequences for mothers and their children [2]. In low- and middle-income countries (LMICs), prevalence of postpartum depression ranges from 3% to 32% [3]. Among adolescents in South Asia, pregnancy is also a risk factor for suicide [4,5]. Fortunately, there has been development and testing of interventions for perinatal depression delivered by nonspecialists in LMICs [6-8]. However, these have shown limited improvement over control conditions [7,8] and lack of long-term benefits [9].

These issues raise questions including the following: (1) are the mothers most likely to benefit from psychological interventions appropriately identified? and (2) are beneficiaries in the interventions achieving the behavioral changes needed for sustained improvements in mental health? Until recently, we have not had feasible methods for collecting data on the daily lives of depressed adolescent mothers in LMICs and the impact of psychological interventions on their self-care, interpersonal relations, and parenting behaviors. Collection of passive sensing data through devices that mothers already used supplemented with unobtrusive additional wearable technology on children has the potential to shed light onto mothers' experiences of and recovery from postpartum depression.

Passive sensing data collection is the accumulation of information from digital devices while users go about their daily lives without requiring their active input [10,11]. Examples of passive data collection from mobile phones include Global Positioning System (GPS) location, physical activity and movement, and amount of time that a device or app is used, such as Web-based social activity. Current health applications of passive sensing data collection include recording physical activity among persons at risk for anemia, neurodegenerative diseases, and cardiometabolic disease [12-16].

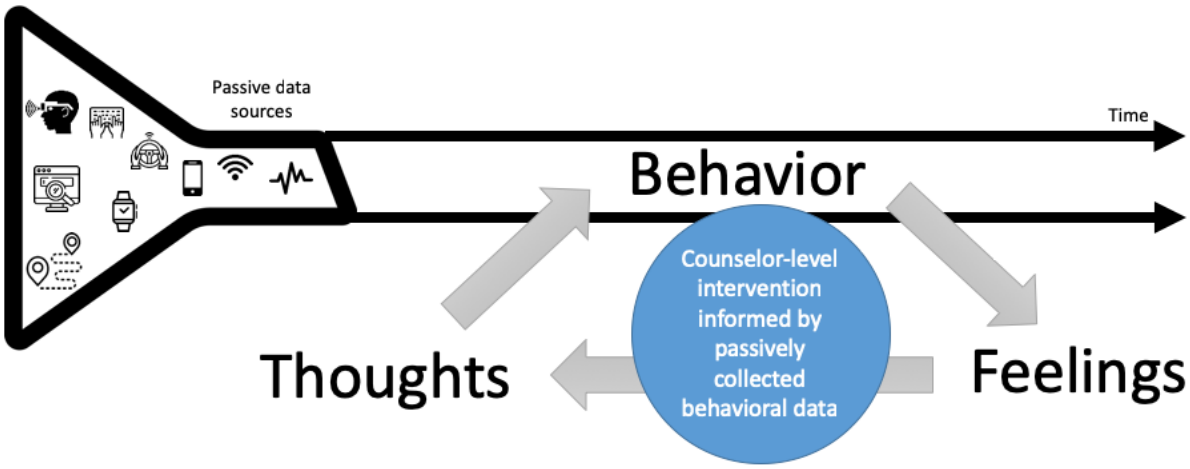
Passive sensing data collection in mental health may help in correct identification of who will benefit from different types of psychological interventions. At present, the field is limited by the approaches used to identify women with postpartum depression in low-resource settings. Self-report checklists—such as the Edinburgh Postnatal Depression Scale [17] and Patient Health Questionnaire (PHQ-9) [18]—are typically used to identify whom to enroll in an intervention [19]. These screening tools are often used as de facto diagnostic tools in LMIC settings where specialists are not available to provide mental health diagnoses [20]. As screening tools, these self-report measures typically have good sensitivity (ie, they identify most persons in need of care, and there are few false negatives); however, they have low specificity (ie, there are many false positives who get included but do not actually have depression) [21]. The problem of these psychometric properties is even greater when working cross-culturally where tools need to be adapted and validated to the local language, culture, and context [22]. One of the reasons for small effect sizes in psychological treatment trials may be that these approaches lead to the inclusion of women with modest distress who would naturally recover in research trials.

Passive sensing data can potentially be used to increase the accuracy of detecting women with postpartum depression who would benefit from psychological interventions. For mental illness, passive sensing data can be used to create digital phenotypes related to activity patterns, sleep, social interactions, and emotional tone of speech [10,23-25]. This approach has shown promise in other neuropsychiatric disorders. An example includes use of passive sensing data to record motion density of activity, circadian rhythm, time away from home, and activity level to identify older adults with risk of early dementia [12]. Similar digital phenotypes are likely to inform postpartum depression risk assessment [26,27].

In addition to helping with diagnosis and symptom monitoring, passive sensing data collection also can be used to improve interventions. For example, monitoring physical activity and

then providing positive reinforcement when activity milestones are achieved has been used for diabetes risk reduction and treatment programs [15]. Similarly, the information garnered through digital phenotyping has the potential to improve the delivery of mental health interventions [28]. In Figure 1, we illustrate how passive sensing data collection from wearable devices can be used to generate behavioral profiles over time.

Figure 1. Model illustrating the role of passively collected behavioral data to enhance behavioral change among treatment beneficiaries in psychological interventions based on behavioral activation and cognitive behavioral techniques.



Intervention providers who are nonspecialists, such as trained lay counselors, could then use the behavioral information when interacting with treatment beneficiaries to explore cognitive and emotional processes (thoughts and feelings) associated with depression. Using behavioral activation or cognitive behavioral techniques, the provider and treatment beneficiary can then collaboratively plan goals for changes in behavior, thoughts, and feelings, with the former monitored through ongoing passive data collection.

Given the need to improve accurate detection of depression through passive sensing data and the potential to incorporate passive sensing data to enhance mental health care, we undertook an exploratory study with wearable digital sensors used by adolescent mothers and their infants in rural Nepal.

Objectives

Our study has 2 objectives. First, we will explore the feasibility and acceptability of passive sensing data collection among depressed and nondepressed adolescent mothers with infants (aged <12 months) and conduct exploratory analyses comparing these data in 4 domains: (1) the overall activity of mothers using accelerometer data from the mobile phones, (2) the geographic range and routine of mothers using GPS data collected from the mobile phones, (3) the time and routine of mothers with their infants using proximity data collected from Bluetooth beacons, and (4) the verbal stimulation and overall auditory environment for mothers and infants using episodic audio recording on mobile phones. Second, we will explore the feasibility and acceptability of collecting passive sensing data from depressed adolescent mothers who are participating in a psychological intervention (behavioral activation) delivered by nonspecialists. These data will then be used to contextualize and personalize the psychological intervention. During the 5 weeks of the psychological intervention, we will document how the passive sensing data are used by the intervention providers in personalizing the intervention, and we will conduct exploratory analyses on changes in the 4 domains over time.

In this study protocol, we describe the global health research setting (Nepal), the psychological intervention (an adaptation of behavioral activation), the technology to be used (a mobile phone given to adolescent mothers and a passive Bluetooth beacon attached to their infants' clothing), the mobile phone app we have developed (which intervention providers can use to integrate passive sensing data into the psychological intervention), and the study components (a participatory research element, a mixed-methods comparison of depressed and nondepressed mothers, and a mixed-methods evaluation of passive sensing data integrated into psychological care).

Methods

Setting

Nepal is one of the poorest countries in South Asia with an economy that relies heavily on remittance from migrant laborers, development aid from high-income countries, and tourism. Nepal has a population of approximately 26.4 million, with 69.1 years life expectancy at birth. The United Nations ranks Nepal 145th out of the world's 188 countries on the Human Development Index, indicating that Nepal has lower life expectancy, education level, and per capita income when compared with other countries [29]. This study will be conducted in Chitwan, a southern district bordering India. The total population of Chitwan is 579,984 (300,897 females) with about 132,462 households [30,31]. Chitwan has a slightly better health and development indicators than the national average. The infant mortality rate is 30.1 per 1000, lower than the national average of 40.5 per 1000. The under-five mortality rates for Chitwan is 38.6 per 1000 (national average is 52.9). Chitwan also has a higher literacy rate than the national average—78.9% in Chitwan compared with the national average of 67% [32].

The estimated age-standardized suicide rate in Nepal is the eighth highest in the world, with the female suicide rate ranking

the third highest [33]. Suicide is a leading cause of deaths among reproductive-aged women in Nepal [34-36], with the highest rates of suicide among women younger than 25 years of age [37]. In Nepal, young mothers are burdened with persistent gender inequity and disproportionate expectations often placed on them following marriage [38-40]. Patrilocal tradition typically requires women to leave their maternal home and assume a relatively low social position in their husbands' households. This can be socially isolating and accompanied by increased exposure to violence [40]. During periods of menstruation, childbirth, and early marriage, some families practice restrictions on women, limiting their geographic movements, physical and social interactions, and religious practices [41]. Social and psychological benefits for women, including upward social mobility, increased fulfillment and life satisfaction, and generativity, are typically contingent upon becoming a mother and, more specifically, giving birth to a son [42,43]. Given the cultural milieu, it is possible that passive sensing technology may help to identify behavioral opportunities to mitigate the risk factors, such as social isolation, associated with adolescent motherhood.

In Nepal, mental health services are restricted to a few government hospitals located in big cities and private hospitals. In Chitwan, mental health services include inpatient and outpatient services available in the district hospital and medical colleges. With 2 psychiatrists and a psychiatric ward in the district public hospital, the district has more capacity compared with most areas in Nepal. Over the past 8 years, Chitwan has been the Nepal implementation district for the Program for Improving Mental Health Care (PRIME), which has contributed to an increase in availability of mental health services. On the basis of PRIME studies, 12-month prevalence of suicidal ideation is 3.5% and attempts are 0.7% in community settings and 11.2% for ideation and 1.2% for attempts among patients presenting to primary care [44]. Moreover, in primary care settings, 11.2% of attendees were found to have depression, but only 1.8% had sought mental health services in primary care [45]. A psychological treatment for postpartum depression was adapted for use in Chitwan through the PRIME activities (additional details are provided in the Intervention section).

Regarding the use and availability of mobile digital technologies, there has been a drastic increase in mobile penetration in the last decade. There are currently 2 leading telecommunication companies in Nepal, along with a few smaller mobile service providers. The nationwide mobile penetration in 2018 was 134% [46]; this number of mobile service plans per person is greater than 1 because many individuals have 2 or more plans with different service providers due to differences in coverage networks.

Intervention

The psychological intervention used in this study is the Healthy Activity Program (HAP) [45]. Although other low-intensity psychological interventions (eg, the Thinking Healthy Program) [6] have been developed for use in South Asia to treat postpartum depression, HAP has shown strong benefit with general depression treatment in India [47] and has added benefit for depression when combined with primary care treatment in Nepal [48]. In addition, HAP has similar psychological elements to the Thinking Healthy Program, with behavioral activation being a major component [47]. Behavioral activation is a type of psychological treatment developed out of cognitive therapy, grounded in learning theory; it has 2 primary components: the use of avoided activities as a guide for activity scheduling and the functional analysis of cognitive processes that involve avoidance [49]. Simplified versions, such as most variants used by nonspecialist providers in LMIC, emphasize the activity scheduling more than the functional analysis.

Through PRIME in Nepal, HAP has been adapted for perinatal depression, and there are numerous government health workers trained in HAP for perinatal depression in Chitwan, Nepal. The HAP intervention that is currently being implemented in Nepal has been divided into 3 phases delivered over 5 sessions (see Textbox 1). Although HAP includes both behavioral activation and problem-solving therapy techniques, the behavioral activation element is the component in which passive sensing data are integrated for this study.

Textbox 1. Phases and sessions of the Healthy Activity Program adapted for use in Nepal.

Phase I: Assessment and psychoeducation

Session 1: Initial assessments for psychosocial well-being and self-care

1. Assurance of confidentiality
2. Assessment of depression risk through the administration of a validated screening tool—Beck Depression Inventory (BDI).
3. Assessment of suicidal risk
4. Assessment of 6 components of self-care (work, rest, nutrition, interpersonal relationships, entertainment, and health)
5. Discussion on the possibility of involvement of family in the Healthy Activity Program (HAP)
6. Homework and discussion on the possible barriers for completion
7. Planning for the next session

Session 2: Psychoeducation based on HAP and self-care

1. Progress review based on BDI and self-care
2. Assessment of suicidal risk
3. Review homework
4. Psychoeducation on HAP and self-care
5. Selection of the activity during the session
6. Involvement of the family member
7. Homework and discussion on the possible barriers for completion
8. Planning for the next session

Phase II: Behavioral activation and problem solving

Sessions 3 and 4: Behavioral activation and problem solving

1. Progress review based on BDI and self-care
2. Assessment of suicidal risk
3. Review homework
4. Problem-solving methods
5. Involvement of a family member
6. Homework and discussion on the possible barriers for completion
7. Planning for the next session

Phase III: Relapse prevention and wrap up

Session 5: Relapse prevention and wrap up

1. Progress review based on BDI and self-care
2. Assessment of suicidal risk
3. Review of skills learned
4. Involvement of a family member
5. Relapse prevention
6. Debrief and wrap up

These sessions have been designed based on HAP as delivered by nonspecialists in LMIC settings [50]. Broadly, each HAP phase has the following content:

Early Phase (Delivered in 1-2 Sessions)

In this phase, the psychosocial counselor engages with the participant and establishes an effective counseling relationship. It also involves describing HAP to the patients and eliciting participant's commitment to continue and complete the counseling sessions.

Middle Phase (Delivered in 3-4 Sessions)

In this phase, the counselor assesses behavioral activation targets and encourages positive behaviors. The counselor, along with the participant, identifies the barriers to activation and ways to

overcome these barriers. This phase also involves helping patients solve or cope with life problems.

Ending Phase (Delivered in 1 Session)

In this phase, the counselor reviews the progress in the last few weeks and discusses with the patient ways to strengthen the gains to prevent relapse.

At present, 20 health facilities in Chitwan have adapted HAP for the treatment of maternal depression. In these settings, HAP is delivered by auxiliary nurse midwives who are part of the formal paid health infrastructure in Nepal. Auxiliary nurse midwives receive 18 months of training after a high school degree that is focused on midwifery, reproductive health including family planning, and community health. For HAP, auxiliary nurse midwives receive 5 days of training on basic psychosocial skills. Those displaying the strongest competency (as evaluated through observed structured role plays) [51] and those with good knowledge and attitudes then participate in 5 days of HAP training. After training, the auxiliary nurse midwives receive in-person supervision from a psychosocial counselor who has completed a 6-month training specialized for Nepal [52]. HAP supervision from psychosocial counselors (and psychiatrists when necessary) occurs approximately biweekly with additional phone and in-person support as needed. The psychosocial counselor supervisors also provide HAP services in areas without trained midwives. For this study, we will include depressed adolescent mothers who are receiving HAP from either an auxiliary nurse midwife or a psychosocial counselor (collectively referred to as *providers* in this protocol).

Conceptual Model

To guide our study, we developed a simple conceptual model (see Table 1) demonstrating how the passive sensing data domains may distinguish differences between depressed and nondepressed adolescent mothers (objective 1) and how domains could be integrated into a brief behavioral activation psychological intervention (objective 2).

Table 1. Conceptual domains related to depression that can be monitored through passive sensing data collection.

Domain	Description	Association with depression	Passive sensing data	Use of passive sensing in the psychological intervention
Physical activity	Time spent inactive, standing, walking, or riding vehicles	Lack of physical activity associated with depression	Accelerometer data from mobile phone provided to mother	Determine targets for physical activity and monitor changes in type and duration of physical activity
Geographic movement	Range and location of daily movement in community	Lack of daily movement outside the home and lack of routine in movement associated with depression	GPS[a] data from mobile phone provided to mother	Identify locations for mood-enhancing activities and monitor movement to those settings
Mother-child interaction	Total time of mother and child together and daily consistency of mother-child routine	Lack of mother's time separate from child (ie, no break from child care responsibilities) and inconsistency of daily routine (ie, erratic schedule) associated with depression	Mother-child proximity measured between mobile phone with mother and passive Bluetooth beacon attached to child's clothing	Identification of times for mood-enhancing activities with and without child and monitoring to increase consistency of daily routine
Interpersonal relations	Exposure to adult verbal communication and verbal communication of child	Lack of exposure to adult verbal communication and lack of verbal engagement with child associated with depression	Episodic audio recordings collected on mobile phone given to mother	Determining targets for social interaction and monitoring adult communication and verbal stimulation of child

[a]GPS: Global Positioning System.

Domain 1: Daily Routine of Physical Activity of Mothers

The Android operating system provides access to several sensors that enable the monitoring of motion. For this study, we used the accelerometer and gyroscope sensors along with the Activity Recognition API, which is built on top of these sensors. The Activity Recognition API automatically detects activities such as walking, riding in a vehicle, and standing. It does this by passing these sensor data into a machine learning model. These data will be interpreted along with GPS data to estimate the frequency, quantity, and type of activity undertaken. We hypothesize that depressed mothers will have less physical activity and less consistent routine of physical activity compared with nondepressed mothers. Self-reported physical limitations are correlated with postpartum depression severity [53]. Prospective studies of women during pregnancy and the postpartum period using self-report measures of daily rhythms demonstrated that women with disrupted sleep and daily rhythms had worsening of depressive symptoms [54]. In the same study, women with histories of mood disorder were more likely to report disrupted rhythms. Wrist actigraphy measurements among postpartum women also showed an association between disrupted routines and poor mental health outcomes; postpartum women with dysrhythmic fatigue patterns reported more stress and less vigor compared with the women where fatigue patterns followed consistent daily cycles [55]. Moreover, clinical insomnia is associated with less regularity in daily physical activity [56]. Therefore, for our first objective, we will explore if women without depression have more stable activity routines compared with women with postpartum depression. For our second objective, we will explore how providers use the activity data to identify and monitor mood-enhancing physical activity. We hypothesize that depressed mothers in the intervention will increase their physical activity and the routinization of their

physical activity over the course of the intervention. This would be expected because 1 element of behavioral activation included in HAP is the scheduling of behaviors that have mood-enhancing qualities.

Domain 2: Geographic Range and Location of Mothers' Routine

This domain will use GPS data collected from a mobile phone. In a study of pregnant mothers, the daily radius of travel was associated with depression symptoms, with greater depression levels associated with more restricted radii of travel [57]. The same study also found that an increase in depressive symptoms predicted smaller radii of travel in subsequent days. For objective 1, we hypothesize that mothers with depression will have more restricted GPS range of movement compared with nondepressed mothers, that is, they will be more isolated and show less movement outside the home. For objective 2, we will explore how providers delivering HAP use the GPS data to identify targets for increased social engagement and physical activity, as well as monitor engagement in mood-enhancing locations identified by the depressed mothers. We hypothesize that depressed mothers in the intervention will show increased GPS geographic range over the course of the intervention.

Domain 3: Duration and Routine of Mothers' Interaction With Their Infants

This information will be generated by a Bluetooth beacon (RadBeacon Dot; Radius Networks, Inc) [58] attached to the child's clothing. Every 15 min, the phone will scan for the presence of the beacon and determine the distance between the devices (proxies for the individuals) using received signal strength indication (RSSI). If the beacon is not detected, the mother and child are assumed to be apart. These data will be used to determine the total amount of time a mother and child spend together each day and the routine of their time together. As mentioned above, routinization of daily behaviors is associated with more positive mood, less fatigue, and lower risk of maternal depression [54,55]. Therefore, in addition to physical routine, we will also capture the daily interaction routine between mothers and infants. We hypothesize that the nondepressed mothers in the study are likely to have more consistent routines over the 2-week period compared with depressed mothers. We also hypothesize that depressed mothers will have less time apart from their child (eg, have no break from child care responsibilities). Self-reported lack of social support for child care activities is correlated with risk and severity of postpartum depression [53,59,60]. High levels of instrumental social support are associated with lower postpartum depression symptom severity [61]. Among low-income Latina women in the United States, lack of partner engagement was associated with greater childcare responsibilities and greater risk of maternal depression [62]. A study in Kenya found that providing social support and addressing caregiver burden were especially important for pregnant adolescents [63]. With regard to the mothers in the psychological treatment, we will explore if providers use the daily proximity data to identify opportunities for mood-enhancing activities. We also hypothesize that mothers will show increasing routinization of their schedule with the child over the course of the intervention.

Domain 4: Verbal Stimulation and Auditory Environment for Mothers and Infants

Using episodic audio recording on a mobile phone, 30 seconds of audio will be recorded every 15 min on the mobile phone provided to the mother. We hypothesize that depressed mothers are more likely to have prolonged periods without verbal communication compared with nondepressed mothers (ie, depressed mothers will have greater silence throughout the day). Audio recordings with human speech will be used as proxy for social interaction. Social isolation is associated with postpartum depression [64]. Loss of social group membership is a risk factor for postpartum depression [65], and this loss of social group is of particular risk for adolescent mothers. In addition, limited verbal engagement between mothers and infants is a manifestation of postnatal depression and predicts poor development for children [66,67]. For objective 2, we hypothesize that depressed mothers in the psychological intervention will show increasing exposure to verbal communication over the course of the intervention. Changes in loneliness and perceived social support are associated with the course of postpartum depression [68]. Women with perinatal depression in therapy showed reduction in depression associated with greater interaction with their infants [69].

Technology

For the project, we are using 2 devices—a mobile phone (Samsung J2 Ace) and a passive Bluetooth beacon (RadBeacon Dot) paired with the phone to serve as a proximity sensor.

Mobile Phone

The Samsung J2 Ace phone is a cost-effective mobile phone (US $114) that is popular in the study setting. Commonly-used low-end mobile phones in Nepal cost US $70-US $120, and therefore the device selected the study was only modestly more expensive than commonly-used devices. Most individuals in the area already own a mobile phone or have a close family member with a mobile phone. Hence, there is minimum risk of stigmatization because of the mobile phone use in the study. We selected the Samsung J2 Ace phone because it is widely available for purchase within Nepal and it was the cheapest option that could effectively run all the features and apps required for the study. The participants will be provided with the phone for the duration of the study. They will return the phone after the data collection. This information is clearly stated in the consent form.

The mobile phone will be used to collect 4 types of data—proximity, episodic audio, activity, and location. To collect these data, we will install our custom-built Electronic Behavior Monitoring app (EBM version 2.0). The EBM app is designed to passively collect data for 30 seconds every 15 min between 4 am and 9 pm. First, the EBM app scans for the presence of advertising packets from the assigned Bluetooth beacon. For episodic audio recording, the microphone in the phone will be used to record 30-second audio clips saved in an MP3 format. The audio data will be collected directly on the mobile phone and uploaded in our cloud-based storage. The processing service that uses machine learning model then converts the audio into a categorical variable with a confidence

score; therefore, the research staff and counselors never hear the audio. We produced a video to explain this process to participants, which was published in a previous paper [70]. Moreover, the participants can request for audio files to be deleted before uploading. Participants can also turn off their phone anytime. We will make the participants aware of these options. We have piloted the approach with participants collecting the audio and deleting it in South Africa [71]. Finally, GPS on the mobile phone will collect the mother's position, and the Activity Recognition API used to record the predicted activity being undertaken at the time of recording. A folder, NAMASTE, is created automatically once the EBM app is downloaded on the mobile phone. All data are recorded within the folder.

Passive Bluetooth Beacon (RadBeacon Dot) (Radius Networks Inc)

The proximity sensor (Figure 2) is fitted to the child's clothing, and the mother is asked to carry the mobile phone to measure the distance between the mother and child. Our assumption is that the beacon is always on the child, and the mobile phone is with the mother. The EBM app will scan for beacons and record proximity information every 15 min, which will give an indication of how often the mother and the child are physically close. In addition, the RSSI gives an approximation of the distance between mother and child. The RadBeacon transmission power was set to show the child as *in proximity* if the distance between phone and beacon was less than 7 m [72]. This distance is affected by the presence of walls, furniture, and other obstacles between the mother and child.

Figure 2. RadBeacon Dot (Radius Networks Inc.).

Use of the RadBeacon Dot was approved by the Nepal Health Research Council for the purpose of this study. RadBeacon Dot also has United States Federal Communications Commission (FCC) certification, a body that oversees the permissible exposure level for all devices with radio frequency. In the United States, the Food and Drug Administration (FDA) relies on FCC for inputs on medical devices [73]. FDA considers devices such as activity trackers as general wellness devices because these devices have "(1) an intended use that relates to maintaining or encouraging a general state of health or a healthy activity or (2) an intended use that relates the role of healthy lifestyle with helping to reduce the risk or impact of certain chronic diseases or conditions and where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition" [74].

Moreover, in our study, RadBeacon is not a medical device used for treatment or for the transmission of health information (eg., temperature, pulse, respiration) from the infant. It is only used to track proximity between mother and infant during daytime hours. Regarding the safety of exposure for infants, the FCC limit for radiation from devices is 1600 mW/kg [75], which equates to approximately 800 mW for a 5 kg infant. The RadBeacon Dot specifications are +4 to −20 dBm, which equates to 2.5 to 0.1 mW. These ranges are comparable to an infant in a house with a standard wireless network and Bluetooth devices.

Preliminary Studies of These Technologies in Nepal

We conducted preliminary studies on the collection of passive sensing data in rural Nepal [70]. We developed videos demonstrating the use of passive sensing data collection in households in Nepal. The videos featured devices for continuous video recording, continuous audio recording, episodic audio recording, as well as wearable cameras placed on the children, Bluetooth beacons placed on the children, and environmental sensors in the home. The videos were shown to female community health volunteers and mothers with young children to assess their perspectives on how passive data collection impacted confidentiality, safety of their children, social acceptability in the family and community, and level of interference on daily activities. In addition, we asked community health volunteers and mothers to identify which types of passive data collection devices they considered most likely to have

utility for improving child development and maternal-child interactions. In rural Nepal, the use of passive Bluetooth beacons placed on the children to monitor when the child was in proximity to the caregiver scored well on these criteria, especially confidentiality and social acceptability. Episodic audio recording had similar perceived utility and social acceptability, but caregivers wanted to assure that confidentiality could be maintained. Regarding safety and low risk of interference in daily life, the episodic audio recording scored better than the proximity beacon. A total of 3 devices (proximity beacon, episodic audio recording, and a child's wearable camera) were then piloted with mothers and children aged 2 to 5 years. On the basis of the results of that pilot study (unpublished data), we selected the proximity beacon and episodic audio recording as appropriate for mothers and their infants aged younger than 1 year in this study.

The StandStrong App

The Sensing Technologies for Maternal Depression Treatment in Low Resource Settings (StandStrong) Platform will be an Android App that the providers can use to access the passive sensing data about participants in HAP. Through this platform, the counselor can review the data collected by the EBM app and provide personalized HAP sessions to the mothers. Additional functionality will be direct text messaging between the mother and the providers, summary of HAP sessions, awards and goals for mothers (contingent to behavioral activation), and psychoeducational materials.

We designed the StandStrong app to compliment HAP. This was not a new intervention that we developed, as HAP was already developed for the treatment of depression in South Asia. However, there was not an app to monitor passive sensing data for incorporation into HAP; this was the purpose of developing the StandStrong App. Moreover, we designed the StandStrong app specifically with the conditions of low-resource settings in mind. The app has low data usage, can be used in older versions of Android, and is translatable into various languages. To the best of our knowledge, this is the first app to bring together this specific package of passive data collection and intervention support in the same platform.

The app has the following 3 main screens (demonstrated in Multimedia Appendix 1):

- Home Page: the homepage works as the newsfeed and provides a list of posts designed to visualize the passively collected data. These posts include proximity, activity, GPS movement, and proximity/daily routine. The counselor will receive a notification when new data are available for the depressed mothers. Moreover, 2 additional posts types are also available that do not rely on passive data. The first is 5 educational posts that are released at a rate of 1 every 3 days. Second, it is possible for the provider to create goals with the client. These can then be reviewed at follow-up visits (Figure 3). All data can be filtered by date and post type.
- Awards: to provide meaningful feedback and encourage positive health behaviors, passive data are automatically reviewed for the attainment of predefined levels of activity. Each of the award categories (Table 2) have 3 levels of attainment that are increasingly challenging to achieve. For example, to achieve level 1 of self-care, the mother needs to spend 1 hour in self-care with another family member or someone else caring for her child. These thresholds were not based on theory or evidence but rather designed to primarily be easily achievable. As data are collected through this pilot study, better calibration of the award levels will be performed. Examples of how these awards are displayed in the app can be seen in Figure 3. A mother will receive an award when the passive data meet the threshold for one of the award categories. The provider is able to see these achievements for all of her clients in the StandStrong app, and the mother is notified of her achievement through an automated message sent to her Viber account (a popular messaging platform in Nepal).
- People: on the People page, the counselor will see a list of all her active clients (Figure 3). This page allows the counselor to enter the client's personal page that has all the available data (awards, proximity, activity, and GPS data).

Figure 3. The StandStrong app. From left to right: Homepage, People, Awards, and Direct messaging.

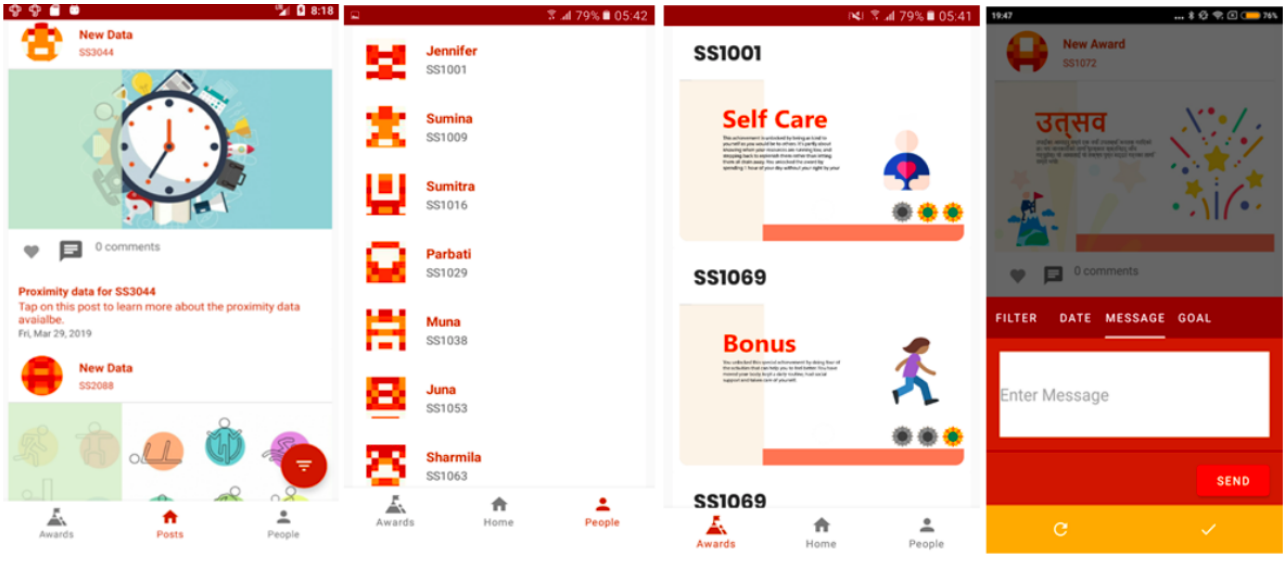


Table 2. Award categories.

Award category and level	Description
Self-care	
Level 1	Spend 1 hour without child on a single day (proximity)
Level 2	Spend 1 hour without child for 2 consecutive days (proximity)
Level 3	Spend 1 hour without child for 4 consecutive days (proximity)
Social support	
Level 1	Hear talking at least 2 times (per 15-min recording) in a single day (audio)
Level 2	Hear talking at least 4 times (per 15-min recording) in a single day (audio)
Level 3	Hear talking at least 6 times (per 15-min recording) in a single day (audio)
Routine	
Level 1	Similar (1-hour variance) pattern of proximity 2 days in a row (proximity)[a]
Level 2	Similar (1-hour variance) pattern of proximity 3 days in a row (proximity)
Level 3	Similar (1-hour variance) pattern of proximity 4 days in a row (proximity)
Movement	
Level 1	Activity other than tilt, sit or still 1 time in a day (accelerometer)
Level 2	Activity other than tilt, sit or still 2 times in a day (accelerometer)
Level 3	Activity other than tilt, sit or still 3 time in a day (accelerometer)
Bonus	
Level 1	L1 for all of the above
Level 2	L2 for all of the above
Level 3	L3 for all of the above

[a]Daily routine was established by looking at the hourly pattern of time spent together with the child and alone. If the pattern was similar across 2 or more days, the award was triggered. *Similar* was defined as the same state (together or alone) appearing 1 hour before, at the same time, or 1 hour later.

Educational Messages

Educational messages, designed to facilitate discussion between providers and mothers, are available within the StandStrong app. Providers can show the messages displayed in the StandStrong app and discuss them with the mothers. The educational messages cover a range of topics such as general depression, perinatal depression, self-care, and sleep regulation. These messages are included in the app with the purpose of psychoeducation for mothers and their family members. It allows participants to learn on their own, as well as discuss these topics in HAP sessions with the counselor.

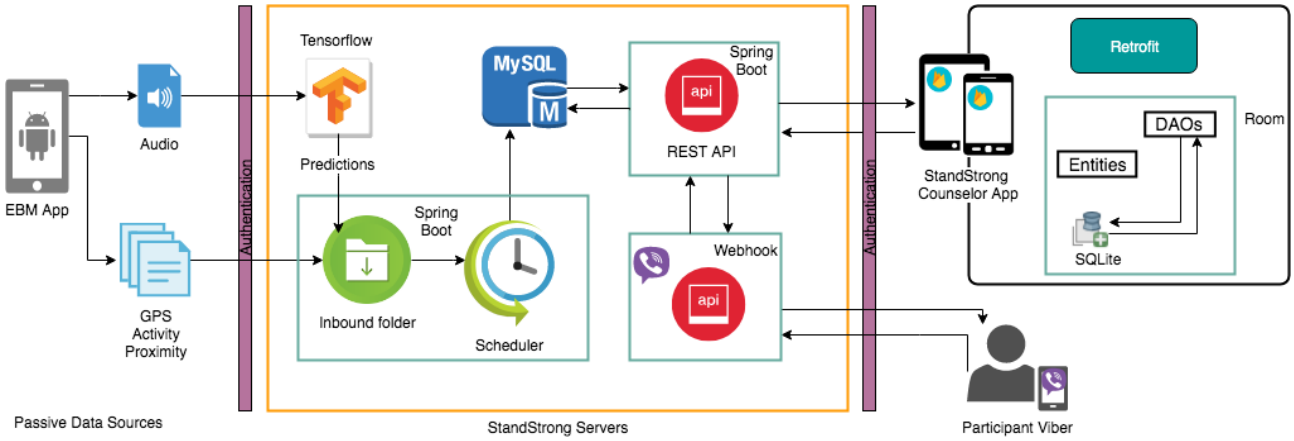
Direct Messaging

The provider can send direct messages to the participants through this feature. Providers use this feature in the app to type out a message, which is then sent to the mother and received on her phone through the Viber app. The participant can respond directly through Viber, and the counselor will receive the message on the StandStrong app (Figure 3).

StandStrong Architecture

The EBM app captures GPS, activity, and proximity data into text files, which are then loaded into the MySQL database through Scheduler. The captured audio .mp3 files need to be processed through Tensorflow, which predicts the social interaction. Thus, produced predictions are loaded into database through Scheduler. The counselor requires the StandStrong counselor app in offline mode while visiting the participant at home where internet is not available. The app gets synchronized to new data when available in the server through REST API. Using Viber API, the counselor and the participants can post or send messages to each other. Figure 4 shows the StandStrong architecture.

Figure 4. The StandStrong architecture. DAO: Data Access Object; EBM: Electronic Behavior Monitoring; GPS: Global Positioning System; API: Application Programming Interface.

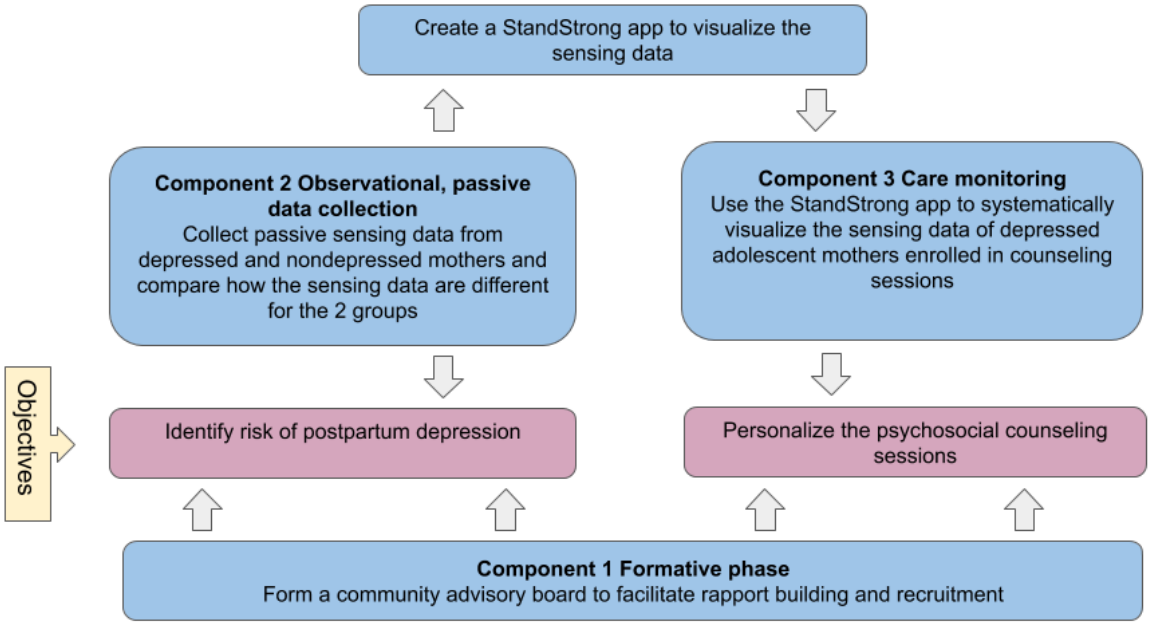


Study Design

The study will be divided into 3 overlapping components (see Figure 5): a qualitative formative component; an observational, passive data collection component; and a care monitoring component. Adolescent mothers (aged 15-25 years) with infants (<12 months) will be recruited for the study. This pilot study will be conducted among participants who will be visiting health facilities in Chitwan, Nepal.

- Component 1: in the formative component, female community health volunteers and auxiliary nurse midwives from 7 health facilities will be invited as the community advisory board members. The community advisory board will facilitate rapport building and networking in health facilities along with inputs on participant recruitment.
- Component 2: employing the recommendations from the community advisory board, we will collect passive sensing data from depressed and nondepressed mothers and compare the data. We will also develop the StandStrong app that will be used to visualize the passive sensing data.
- Component 3: the final component will be the care monitoring phase where we will use the StandStrong app to systematically visualize the passive sensing data of depressed adolescent mothers enrolled in counseling sessions. The providers will have access to the passive sensing data, which can then be used to provide tailored counseling sessions to the mothers.

Figure 5. Conceptual map of the study.



Component 1

In the formative phase, the community advisory board will be established to identify the feasibility and acceptability of using sensing technology among adolescent and young mothers in the community. In addition, community advisory board members will assist in understanding the cultural context, particularly, the experiences of adolescent mothers in the community and the use of mobile technology among young mothers.

Participants

The community advisory board will include auxiliary nurse midwives and female community health volunteers currently working in the 7 health facilities. They were included on the basis of the following criteria:

- Preferably aged younger than 30 years.
- Working in the same community for the past 2 years at least.
- Motivated and working with HAP, or experience working on similar mobile health (mHealth) projects

Throughout the project, we will also recruit adolescent mothers to join the community advisory board after they have completed the study procedures.

Data Collection

The community advisory board meetings, facilitated by the research staff, will be held at regular intervals throughout the study period to understand perceived challenges for adolescent mothers and the potential for using technology to improve mental health outcomes. In addition, we will elicit feedback throughout the iterative development of the StandStrong app. Focus group discussion data will be collected during the first community advisory board meeting, along with field notes and meeting minutes from each of consecutive meetings. These data will be used alongside the other data in components 2 and 3 to assess the overall feasibility and appropriateness of the platform and study.

Component 2

Following the formative phase, we will collect passive sensing data from both depressed mothers (n=20) and nondepressed mothers (n=20) to assess the differences in passive data between these groups. We will also determine the feasibility, acceptability, and utility of the data based on the feedback from the adolescent mothers and community advisory board members.

Participants

For the observational passive sensing data phase, female research assistants will reach out to the adolescent mothers in postnatal clinics and immunization camps and then, on receiving consent, administer Patient Health Questionnaire (PHQ-9) for screening. Mothers between the age of 15 and 25 years with infants up to 12 months of age will be considered for recruitment. Research assistants will make home visits for the mothers who agree to participate. During the time, research assistants will discuss the technology and get family consent, which is considered integral in the cultural context. For adolescent mothers aged younger than 18 years, the parental permission form will also be signed at this time. Women with a PHQ-9 score higher than or equal to 10 will be recruited as depressed mothers and those below 7 or equal as nondepressed mothers. We will collect passive sensing data from both depressed and nondepressed mothers for 2 weeks. We will compare the data for these 2 groups.

Quantitative Data Collection

A series of mental health and other assessment measures will be used for monitoring mental health and triangulation with sensing data. All tools underwent a standardized process of transcultural translation and validation that our team has used extensively in Nepal [76-79]. This procedure involves producing a Nepali translation, followed by review with Nepali mental health experts. Tools are then evaluated through focus group discussions with Nepali beneficiary populations. A back translation is then reviewed by the study team to compare with the original tool. At each stage, comprehensibility, acceptability, relevance, and completeness of tools are evaluated to determine cultural equivalence. This optimizes semantic, content, construct, and technical equivalence of the items. This assures that somatic complaints, terminology for suicide and self-harm, and idioms of distress are culturally relevant. We also include specific Nepali cultural concepts of distress, such as *heart-mind problems* and ethnopsychological models that are more culturally acceptable to discuss than stigmatized psychiatric terminology [80-83].

1. PHQ-9: the PHQ-9 measures depression symptom severity with 9 items, each with 3 response options and a score range from 0 to 27. It will be administered at the time of study screening. From the validation study in primary care settings in Chitwan, a cutoff score of 10 or more had 94% sensitivity and 80% specificity, and internal consistency of alpha of .84 [80].
2. Beck Depression Inventory (BDI): the BDI is a clinical screening tool used for depression and consists of 21 self-reported items each scoring 0 to 3, with a maximum score of 63. The tool has been validated in Nepal using the local Nepali language among clinical and community participants in urban and rural settings with a cutoff score of 20 [78]. The BDI is also routinely used in clinical practice in Nepal as a measure of symptom improvement. The area under the curve that captures the amount of correctly classified persons in this case for moderate depression was 0.919 (95% CI 0.878-0.960) for the BDI; internal reliability was also high, BDI Cronbach alpha=.90. On the basis of clinical validation of the BDI in Nepal, a score of 20 or higher suggests moderate depression with the need for mental health intervention (sensitivity=0.73 and specificity=0.91). The two-week test-retest reliability Spearman-Brown coefficient for the BDI was 0.84 [84].
3. World Health Organization Disability Assessment Scale (WHODAS): the WHODAS 2.0 12-item tool measures difficulty in daily functioning, including self-care and home activities. Items are scored on a Likert scale from 1 (*none*) to 5 (*extreme/cannot do*), with possible range from 0 to 48 where a higher score indicates more functional difficulty. The WHODAS has been used in a range of settings and in previous research in Nepal, including interventions that have focused on behavioral activation. Internal consistency for the WHODAS in the Chitwan population is alpha=.84 [48]. These markers will help in tracking participant improvement in daily functioning because of the support of providers and the use of technology.
4. Home Observation Measurement of the Environment (HOME): the HOME is a 45-item measure of the child's exposure to stimulating interactions, environments, and emotional support [85,86]. The measure is comprised of 6 subscales including responsivity, acceptance, organization, learning materials, involvement, and variety and are elicited

with a combination of rater observations during the home visit and direct elicitation of self-report from the parent. The HOME scale has been used extensively in South Asia [87-89] and was adapted to ensure appropriateness for the Nepali context.

5. Observation of Mother and Child Interaction (OMCI) [88,90-92]: the OMCI is an observational tool that was developed and used extensively in South Asia to assess mother-child interactions in a live-coded format. In its development, the tool had high interobserver reliability and was significantly correlated with the responsivity and involvement subscales of the HOME [91]. The tool measures 4 typical domains of maternal responsive behaviors (responsivity, emotional-affective support, support for infant attention, and language stimulation). The tool includes 18 items, with a range from 0 to 54, and higher scores indicate more positive interaction. Rather than standard assessments that require video recording in laboratory-like settings, this technique was adapted for more feasible and rapid use in low-income contexts. Instead of requiring a video, it uses a live coding framework. The OMCI is conducted by a trained female research assistant during the second or third home visit to the newly recruited mother. The mother is given soft toys appropriate for a Nepali infant (baby rattles, trumpet, and squeeze animals toys for 3- to 9-month-old babies; car, bigger rattles, and pinwheel for 6- to 12-month-old babies) and instructed to play with her child as she normally would for 5 minutes. After the first minute, the research assistant counts the instances in which a particular behavior occurs (eg, intrusive behaviors). In addition to the live coding, the interaction will be video recorded. We are using the OMCI in a qualitative manner to benchmark the technology findings, particularly related to verbal interactions and interaction quality (elicited through the episodic audio recording with subsequent machine learning) and therefore provide more reliable results of our findings. Thus, we expect that mothers with less verbal interaction (as recorded by the passive sensing domain—audio with conversations) and less consistent beacon proximity data (as determined by the passive sensing domains—time spent with and away from infant) will have lower OMCI scores on the corresponding items/domains (OMCI domains—verbal statements and communication).

Qualitative Data Collection

1. Key informant interviews will be conducted with each woman enrolled in component 2 within the first 3 days of passive data sensing data collection and again at end line (on the 14th day). The first key informant interview elicits the experience of adolescent mothers in relation to her pregnancy, childbirth, and depression. The interview also explores her perceptions and experiences of self-care, help seeking, and interpersonal relationships. This key informant interview is particularly helpful for our team to optimize the passive sensing data for the culture and context of its users. The second key informant interview will be conducted on the use of technology. Interviews will elicit several domains about the feasibility, acceptability, barriers, and facilitators of collecting passive sensing data.
2. Daily diary elicitation will be done by trained Research assistants with the mother recounting her activity; location; child's activity, location, and caregiver; and who else was with her together on the hourly basis for a single day in the past week. It also elicits from the mother the time she awoke in the morning, went to bed in the evening and approximately when she fell asleep. Interruptions and triggers for waking up were also documented. The research assistant also asks the mother to self-evaluate her mood during the morning, afternoon, and evening in the previous day using 5 emoticons ranging from sad to happy. This activity allows us to triangulate the passive sensing data collected from the mother for accuracy.

Component 3

On the basis of the feedback from components 1 and 2, we will start the care monitoring phase (component 3) where we will provide the providers with the passive sensing data which will be incorporated during HAP sessions. With these data, the providers can provide tailored counseling sessions to the adolescent mothers with the risk of depression. We will develop the StandStrong app, which will be used to systematically visualize the passive sensing data. In the care monitoring phase, we will refer the depressed adolescent mothers recruited in the observational phase to HAP counseling sessions. We will provide the providers with a tablet with StandStrong app to access passive sensing data of the depressed mothers. The HAP providers can then provide tailored HAP sessions based on the case's passive sensing data as visualized in the StandStrong app. In addition, we will conduct exploratory analyses on changes over time of the behaviors monitored by the passive sensing data.

Participants

We will use the same recruitment criteria for component 3 as was used for depressed mothers in component 2. Participants from component 3 will also be analyzed as cases in Component 2 using the first two weeks of their passive data collection. Therefore, we anticipate that some of the 20 depressed women recruited for component 2 will also be included in component 3.

Quantitative Data Collection

All the quantitative data collection used in component 2 will also be used for component 3. In addition, because component 3 involves a therapeutic intervention (HAP), the BDI is also ideal to measure changes in symptom severity over the course of implementation. The BDI will be administered weekly for approximately 6 to 8 weeks.

Qualitative Data Collection

Similar to component 2, for component 3, key informant interviews will be conducted with each woman within the first 3 days of passive data sensing data collection and again at end line (after approximately 5 weeks). This key informant interview is particularly helpful for our team to optimize the passive sensing data and the StandStrong app for the culture and context of its users. The second key informant interview will be

conducted on the use of technology and the integration of passive sensing data in StandStrong app. Interviews will elicit several domains about the feasibility, acceptability, barriers, and facilitators of using and understanding the passive sensing data used for the intervention.

Data Analysis

Qualitative Data Analysis

Informed consent will be documented from each participant. All qualitative interviews will be conducted in Nepali, transcribed verbatim (also in Nepali), and then translated into English, preserving culturally meaningful terms. Textual transcripts will be imported into qualitative data analysis software and systematically coded for the themes described above. Content analysis will be used to reduce, synthesize, and provide rich descriptions for StandStrong's acceptability and feasibility, particularly to assess if, and how, the approach can be brought to a larger scale. We will systematically triangulate each passive data collection strategy with the appropriate qualitative and quantitative data (Table 3). The GPS and beacon proximity data will be triangulated with the daily diary elicitation. The Episodic Audio Recorder (EAR) output will be triangulated with the OMCI and HOME. Finally, the exit interview asks the mother to tell us if she thinks her data (seen in the StandStrong app) is accurate and asks her to interpret and describe her behaviors.

Table 3. An overview of the data collection methods and outcome measures.

Domain	Data type	Methods	Passive data	Measures	Components		
					I	II	III
Passive sensing data	Quantitative	GPS[a] (mobile phone)	Movement	Amount of time at the house	—[b]	x[c]	x
Passive sensing data	Quantitative	GPS (mobile phone)	Movement	Time spent outside the house	—	x	x
Passive sensing data	Quantitative	Accelerometer (mobile phone)	Activity	Activity—time spent standing, walking, running.	—	x	x
Passive sensing data	Quantitative	Proximity beacon (proximity beacon)	Proximity	Time spent with the child	—	x	x
Passive sensing data	Quantitative	Proximity beacon (proximity beacon)	Proximity	Time spent away from child (self-care)	—	x	x
Passive sensing data	Quantitative	Proximity beacon (proximity beacon)	Proximity	The consistency of interaction between mother and child	—	x	x
Passive sensing data	Quantitative	Episodic audio recorder (mobile phone)	Audio with conversations	Social interaction (conversation)	—	x	x
Environment	Quantitative	Home Observation Measurement of the Environment inventory	N/A[d]	A 45-item tool to assess the home environment in terms of responsivity, acceptance, organization, learning materials, involvement, and variety	—	x	x
Environment	Quantitative	Observation of Mother-Child Interaction	N/A	An 18-item tool to assess the quality of interaction between mother and child.	—	x	x
Environment	Qualitative	Day in Life	N/A	An hour-by-hour description of participant's activities over an average day (4 am to 10 pm) to record scheduled activities.	—	x	x
Feasibility, acceptability, and utility	Qualitative	Focus group discussion with community advisory board members	N/A	—	x	x	x
Feasibility, acceptability, and utility	Qualitative	Key informant interview with adolescent mothers on motherhood	N/A	—	—	x	x
Feasibility, acceptability, and utility	Qualitative	Key informant interview with providers	N/A	—	—	—	x
Feasibility, acceptability, and utility	Qualitative	Key informant interview with adolescent mothers on technology	N/A	—	—	x	x

[a]GPS: Global Positioning System.

[b]Passive data will not be collected.

[c]Passive data will be collected.

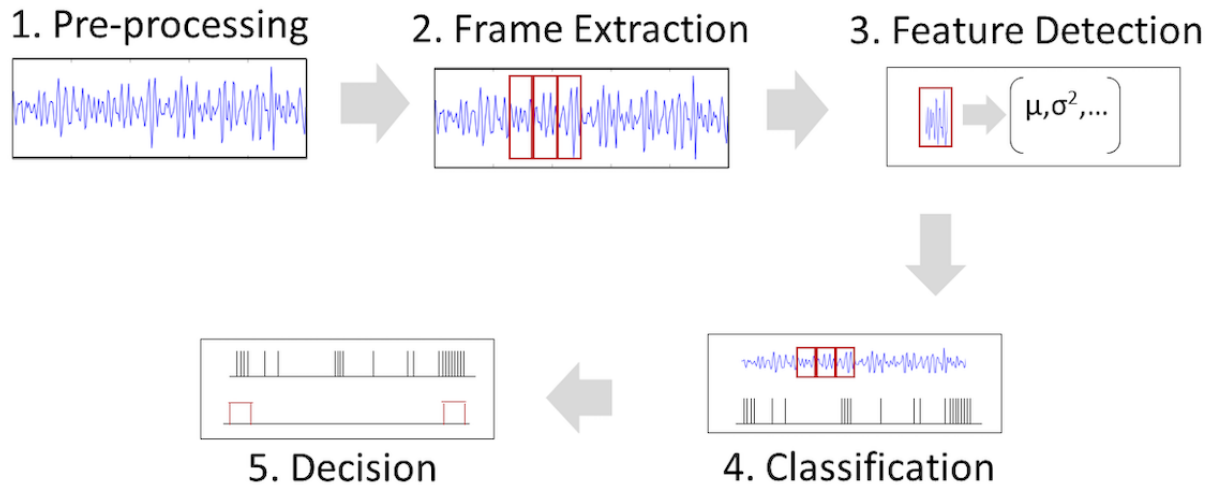
[d]N/A: not applicable.

Quantitative Data Analysis

This project will be dealing with quantitative unstructured data produced passively by a range of sensors. These sensors include proximity, GPS location, and episodic audio recordings. Working and analyzing these data are complex, and many of the analytic methods are still experimental and evolving. There is however an agreed-upon analytic pipeline that will be used for all sensor data collected in this study (Figure 6).

1. Preprocessing: the first step in the analytic plan is to process the raw data files and prepare them for the subsequent steps. During this stage, data are cleaned, and missing values and outliers are addressed through mean replacement or other similar techniques. Data are restructured from a raw comma-separated values into a data frame that can be easily manipulated in Python using a machine learning package such as scikit-learn or Tensorflow.
2. Frame extraction: as the sensor data are time stamped and the feature of interest (such as a spoken word) occurs over a number of seconds, data need to be split into segments using a sliding time window. The literature suggests appropriate window lengths for a different feature. For example, a laugh may last 5 seconds while a cough usually occurs over a period of only a second. This window is then passed over the raw data splitting an uninterrupted data signal into segments of homogeneous content.
3. Feature detection: feature extraction is an important analysis stage. During this stage, we will extract a set of data elements that provide representative characteristics of the frame. The aim of this analysis is to form a feature vector for each frame that can serve as an input to the classifier. Feature extraction can also be viewed as data rate reduction procedure and allows the classification analysis to be based on a reduced set of feature vectors. We will extract 2 types of features from the audio sensor data collected in this study, namely temporal and spectral features. We plan to use Fast Fourier Transform to extract temporal features include zero-crossing rate, short-time energy, energy entropy, root mean square, and autocorrelation. Spectral features of the raw sensor data will be extracted using mel-frequency cepstrum coefficients.
4. Classification: classifiers can be divided into 2 groups—classifiers that use supervised learning (supervised classification) and unsupervised learning (unsupervised classification). In supervised classification, examples of the correct classification are provided to the classifier. On the basis of these examples, which are commonly termed as training samples, the classifier then learns how to assign an unseen feature vector to a correct class. Examples of supervised classifications include Hidden Markov Model, Gaussian Mixture Models, K-Nearest Neighbor, and Support Vector Machines. In unsupervised classification or clustering, there is neither explicit teacher nor training samples. This study will make use of supervised learning with data taken from the early stages used to build and train a model capable of classifying unseen sensor data.
5. Decision making: decision making is the final stage in the analytic pipeline. In this study, we will compute simple summary statistics of interest that can be fed back to participants in a meaningful way. These statistics will include percent time with child percent verbal stimulation of child and percent of distressed vocalizations.

Figure 6. Analytic pipeline for sensor data.



Data Validation

We aim to validate the sensing data using qualitative and quantitative data collected from the study tools. Our sensing data (activity, GPS, and proximity) will be validated using qualitative (Day in Life) and quantitative (HOME, OMCI, WHODAS, BDI, and PHQ) tools. Our team has included several other measures to benchmark the passive sensing data particularly because the novel technology has few markers of precision and sensitivity. Finally, we expect that mothers with fewer stimulating occurrences (described above with the EAR) and mothers with prolonged time with their infant (proximity) to have lower HOME and OMCI scores.

Ethical Approval

The study has been granted ethical approval by the Nepal Health Research Council (327/2018) and George Washington University Institutional Review Board (#051845).

Results

The study is currently underway, and recruitment for participants is open. A community advisory board for the study has been formed. The community advisory board reviewed the objectives and key components of the protocol. The community advisory board also reviewed the technology to be used by observing videos demonstrating the technology [70] and through a live demonstration of the technology. The community advisory board provided input on methods of recruitment and how best to explain the study to adolescent mothers and their in-laws with whom they reside. In addition, based on feedback from the community advisory board, local research team, and initial participants, the final mental health evaluation tools (PHQ-9 for screening and BDI for symptom evaluation) were selected.

Discussion

Given the burden of untreated depression globally, especially among adolescents in LMIC, there is a need to identify approaches to improve identification of who will benefit from psychological services and to make those services more effective. Passive sensing data have the potential to improve accuracy of detection and enhance personalization of services, thus leading to greater effectiveness and sustainability of mood and behavioral changes. Upon completion of this study, we will have greater knowledge of what is feasible and acceptable for the use of mobile technology to collect passive sensing data among adolescent mothers with infants. We also will have results of exploratory analyses comparing depressed and nondepressed mothers on passive sensing data outcomes to determine what domains most accurately identify depression. Moreover, at the culmination of the study, there will be a mobile platform for nonspecialists and the mothers they are treating. Successful completion of this study will thus advance knowledge about postpartum depression and establish new applications of technology and data to improve the lives of adolescent mothers. At a policy level, Nepal formulated a National Electronic Health Strategy in 2017 and is committed to integrating electronic and mobile technologies to increase effectiveness and access to health care services [93]. Given that projects in Nepal such as PRIME have successfully integrated nonspecialists in mental health care service delivery [48], the findings from this pilot study can advance the benefits of mobile technology for psychosocial counseling services delivered by the nonspecialists.

In addition to the service delivery benefits in LMICs, the methods of the proposed study have implications for mental health interventions in the high-resource settings as well. In high-income countries, there has been an explosion of mHealth apps addressing mental health and psychological well-being [94]. However, most of these apps are self-directed and do not involve a therapist. A recent review of cognitive behavioral therapies found that unguided self-help, such as using an app without also having a human component, does not have comparable benefit to individual, group, phone-based, and guided self-help that includes a human interaction [95]. One of the challenges is that most therapists in high-income countries are not trained on how to incorporate mHealth data into existing therapies [94-96]. The StandStrong app provides a framework for therapists to work with clients, measure progress, and identify opportunities for therapeutic goals. To date, apps for physical health condition (eg, diabetes and cardiovascular disorders) have demonstrated added value when the health professionals are engaging with the app alongside patients [97,98]. Similarly, the StandStrong app could provide a platform for greater collaboration between clients and providers, rather than an interface that is only used by clients. Moreover, within the field of mental health, most outcome and process measurements continue to rely on self-reports. The United States National Institute of Mental Health has called for more objective measures of what happens in mental health interventions [99]. This study advances work in objective measurement by tracking behavioral changes over the course of an intervention. This will shed light on what aspects of behavioral change are linked with improved mood and well-being.

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Authors' Contributions

BAK, AvH, and AH conceptualized the study. AH designed the qualitative data collection and analysis plan. AvH and PB conceptualized and designed the StandStrong architecture. AvH designed the analytic pipeline for the passive sensing data. All authors contributed to the protocol development; AP drafted the study protocol, and all authors contributed to protocol revision. SMM coordinated the field activities and implemented the study protocol. AP and BAK drafted the manuscript, and all authors contributed to manuscript sections and revision of the final text. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
StandStrong app demo.
[MP4 File (MP4 Video)51053 KB - resprot_v8i9e14734_app1.mp4]

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Abbreviations

BDI: Beck Depression Inventory
EAR: episodic audio recorder
EBM: electronic behavior monitoring
FCC: Federal Communications Commission
FDA: Food and Drug Administration
GPS: Global Positioning System
HAP: Healthy Activity Program
HOME: Home Observation Measurement of the Environment
LMIC: low- and middle-income countries
mHealth: mobile health
OMCI: observation of mother-child interaction
PHQ-9: Patient Health Questionnaire
PRIME: Program for Improving Mental Health Care
RSSI: received signal strength indication
StandStrong: Sensing Technologies for Maternal Depression Treatment in Low Resource Settings
WHODAS: World Health Organization Disability Assessment Scale

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Protocol

A Fully Integrated Real-Time Detection, Diagnosis, and Control of Community Diarrheal Disease Clusters and Outbreaks (the INTEGRATE Project): Protocol for an Enhanced Surveillance System

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Abstract

Background: Diarrheal disease, which affects 1 in 4 people in the United Kingdom annually, is the most common cause of outbreaks in community and health care settings. Traditional surveillance methods tend to detect point-source outbreaks of diarrhea and vomiting; they are less effective at identifying low-level and intermittent food supply contamination. Furthermore, it can take up to 9 weeks for infections to be confirmed, reducing slow-burn outbreak recognition, potentially impacting hundreds or thousands of people over wide geographical areas. There is a need to address fundamental problems in traditional diarrheal disease surveillance because of underreporting and subsequent unconfirmed infection by patients and general practitioners (GPs); varying submission practices and selective testing of samples in laboratories; limitations in traditional microbiological diagnostics, meaning that the timeliness of sample testing and etiology of most cases remains unknown; and poorly integrated human and animal surveillance systems, meaning that identification of zoonoses is delayed or missed.

Objective: This study aims to detect anomalous patterns in the incidence of gastrointestinal disease in the (human) community; to target sampling; to test traditional diagnostic methods against rapid, modern, and sensitive molecular and genomic microbiology

methods that identify and characterize responsible pathogens rapidly and more completely; and to determine the cost-effectiveness of rapid, modern, sensitive molecular and genomic microbiology methods.

Methods: Syndromic surveillance will be used to aid identification of anomalous patterns in microbiological events based on temporal associations, demographic similarities among patients and animals, and changes in trends in acute gastroenteritis cases using a point process statistical model. Stool samples will be obtained from patients' consulting GPs, to improve the timeliness of cluster detection and characterize the pathogens responsible, allowing health protection professionals to investigate and control outbreaks quickly, limiting their size and impact. The cost-effectiveness of the proposed system will be examined using formal cost-utility analysis to inform decisions on national implementation.

Results: The project commenced on April 1, 2013. Favorable approval was obtained from the Research Ethics Committee on June 15, 2015, and the first patient was recruited on October 13, 2015, with 1407 patients recruited and samples processed using traditional laboratory techniques as of March 2017.

Conclusions: The overall aim of this study is to create a new One Health paradigm for detecting and investigating diarrhea and vomiting in the community in near-real time, shifting from passive human surveillance and management of laboratory-confirmed infection toward an integrated, interdisciplinary enhanced surveillance system including management of people with symptoms.

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KEYWORDS

gastrointestinal diseases; syndromic surveillance; microbiology; diarrhea; vomiting

Introduction

Background

Diarrheal disease, affecting 1 in 4 people in the United Kingdom annually [1], is the most common cause of infectious disease outbreaks in community and health care settings. Traditional surveillance methods tend to detect point-source outbreaks of diarrhea and vomiting; however, they are less effective at identifying low-level and intermittent contamination of the food supply, unless the organism is very rare. Furthermore, it may take up to 9 weeks for infections to be confirmed by a reference laboratory, reducing recognition of *slow-burn* outbreaks that can affect hundreds or thousands of people over a wide geographical area.

There is a need to address fundamental problems inherent in traditional surveillance for diarrheal disease. First, surveillance depends on the examination of stool samples obtained from symptomatic patients attending their general practitioner (GP). The submission practices and selective testing of samples in laboratories can vary and potentially fragment current laboratory-based surveillance systems. Furthermore, as fewer people present in person to their GP, laboratory-based systems have become less sensitive; the *hidden* burden of disease has increased [1]. Second, limitations of traditional microbiological diagnostic methods mean that the etiology of diarrhea in most cases remains unknown. Third, diagnostics are conducted in a hierarchical manner (local detection, confirmation, and typing centrally at national reference laboratories), which can take several days and can be delayed during busy periods such as when an outbreak investigation is underway. Finally, although many diarrheal diseases are zoonotic, human and animal surveillance systems are poorly integrated, meaning that identification of zoonotic events, including emergence of new or antibiotic-resistant strains, is delayed or missed altogether.

Overall Study Aim

The overall aim of this study is to create a new *One Health* paradigm for detecting and investigating diarrhea and vomiting in the community in near-real time, shifting from passive human surveillance for gastrointestinal (GI) illness and management of laboratory-confirmed infection toward an integrated, interdisciplinary enhanced surveillance system including management of people with symptoms.

Contribution to the Field

The comparison of the use of syndromic surveillance for cluster detection and targeted sampling within the community with the use of traditional surveillance will provide a series of improvements to the surveillance of GI disease. We hypothesize that enhanced GI surveillance will allow the following:

- Faster identification of outbreaks of GI disease
- More accurate characterization of the *hidden* burden of disease (underreporting of episodes of illness in which patients do not visit GPs in person). This will result in an observed increase in the incidence of outbreaks
- Identification of a greater number of routes for transmission of pathogens that cause GI illness.

The integration of human and animal syndromic surveillance systems and the use of modern microbiological methods within this project are hypothesized to facilitate (1) faster detection of zoonotic transmission events; (2) earlier identification of a greater spectrum of disease-transmitting pathogens, reducing the diagnostic gap for GI disease; and (3) a reduction in the numbers of false-positive and false-negative stool samples.

There will be differences in the costs and benefits of using improved surveillance methods to detect outbreaks of GI disease earlier compared with using traditional surveillance methods. Potentially, these differences could be in parameters relating to host-pathogen interactions; rate parameters that define the transition of patients among relevant states (eg, susceptible,

diseased, and symptomatic and/or infectious); test characteristics, defined by sensitivity, specificity, and positive and negative predictive values; costs (associated with screening, patients' use of National Health Service [NHS] community, primary and secondary care services, treatments, and other investigations); health outcomes (defined by health state utilities); personal social services; days absent from work or education; and other potential cost impacts.

Overall Objectives of the Research Program

The overall objectives of this research program are to (1) develop and implement new sampling and microbiological testing algorithms, including strategies for pathogen discovery and evolutionary biology; (2) run the new system alongside the existing system to assess its performance against a set of outcome-based indicators including time to detection of event, compliance with sampling among people with symptoms, numbers of false-positive and false-negative stool samples, and diagnostic yield; and (3) determine the costs and benefits of the new system.

Methods

Setting

The setting is the North West area of England (population 7.1 million).

Case Recruitment and Informed Consent

A total of 4 data streams will feed in real time into the new surveillance program. They are NHS 111 telephone triage data on symptoms of vomiting and diarrhea (a real-time syndromic surveillance system operated by Public Health England [PHE]), data from the Small Animal Veterinary Surveillance Network [2], and *Salmonella* data from the Animal and Plant Health Agency (APHA).

The fourth data stream will be derived from general practices in the Royal College of General Practitioners' Research and Surveillance Centre National Monitoring Network (RCGP RSC NMN) [3]. Members of the public with symptoms of acute gastroenteritis including a case definition of vomiting and diarrhea who seek health advice from general practices in the RCGP RSC NMN will be invited to submit a stool sample for microbiological examination. Their consent for this procedure will be sought because normal care would not necessarily entail stool sampling for most patients unless their symptoms were severe or had persisted for a long time. It is possible that most patients will be recruited as part of a telephone consultation with a member of their primary health care team (physician assessment by telephone). The primary health care team will arrange for the patient to receive through the post an invitation letter, an information sheet about the study, a consent form, a stool sampling kit with a reply-paid envelope, and a short Public Health Acute Gastroenteritis questionnaire (which is part of routine public health practice) with a reply-paid envelope. Patients who present at a general practice in the RCGP RSC NMN will receive these items in person. Patients who consent to take part and provide a stool sample will be recruited into the study. Consent statements agreed to in the study consent form include acknowledgment that taking part in the study is voluntary and that consenting patients can leave at any time. Figures 1 and 2 describe the study recruitment procedure, processes, and data flows using flow diagrams.

We aim to recruit 6000 participants. This will allow us to detect the period (annual) prevalence of symptomatic GI infection in the community of 20% ± 1%.

Sample Processing

On receipt at 1 of the 3 diagnostic laboratories taking part (Royal Liverpool and Broadgreen University Hospitals NHS Trust, Central Manchester University Hospitals NHS Foundation Trust, or Lancashire Teaching Hospitals NHS Foundation Trust), the stool sample will be divided into 2 parts. One part of the sample will be processed according to routine clinical practice at each of the 3 laboratories. The other half will be processed with a rapid first-line diagnostic screen, using a molecular multiplex real-time polymerase chain reaction (PCR) assay (a commercially available CE-marked kit [Luminex xTAG Gastrointestinal Pathogen Panel, xTAG GPP] [4]), which incorporates most of the major community GI pathogens relevant to the United Kingdom. This will be complemented by tests for Enteroaggregative *Escherichia coli* and Sapovirus, which have been incorporated into the xTAG GPP assay, using assays already developed for PHE's Olympics Response [5]. Downstream from the rapid xTAG GPP diagnosis, an algorithm for testing stool samples from presumed outbreaks using next-generation sequencing technologies will allow for molecular characterization of known pathogens. Where a pathogen has not been identified (likely in 60% of samples), samples from clinically severe outbreaks will be fast-tracked and characterized using a relatively low-throughput platform for combined RNA/DNA viromes and bacterial metagenomes. If they are from less clinically urgent cases, they will be sequenced at reduced cost on a high-throughput platform.

If a patient does not wish to take part in the study but does submit a stool sample, this case will be processed according to routine clinical practice.

All results will be reported to the patient's GP. Results from the Luminex assays will be issued as an interim report through *Telepath*, which is the routine electronic reporting system between diagnostic laboratories and general practice, and the results of the routine clinical practice assays will be issued as a final report through *Telepath*. In each laboratory, an experienced consultant medical microbiologist, who is a coinvestigator on the grant with research time costed into it, will be available to discuss any discrepant results with the patient's GP. The most likely scenario is that a stool sample that provides negative results using traditional methods will provide positive results using the xTAG GPP. This is to be expected because the xTAG GPP, which is a multiplexed PCR, will detect the presence of pathogen DNA/RNA in stool even if an organism has died-off in the sample during transit to the laboratory.

Figure 1. Patient recruitment flow diagram and study processes for the INTEGRATE project. ASAP: as soon as possible; xTAG GPP: Luminex xTAG Gastrointestinal Pathogen Panel.

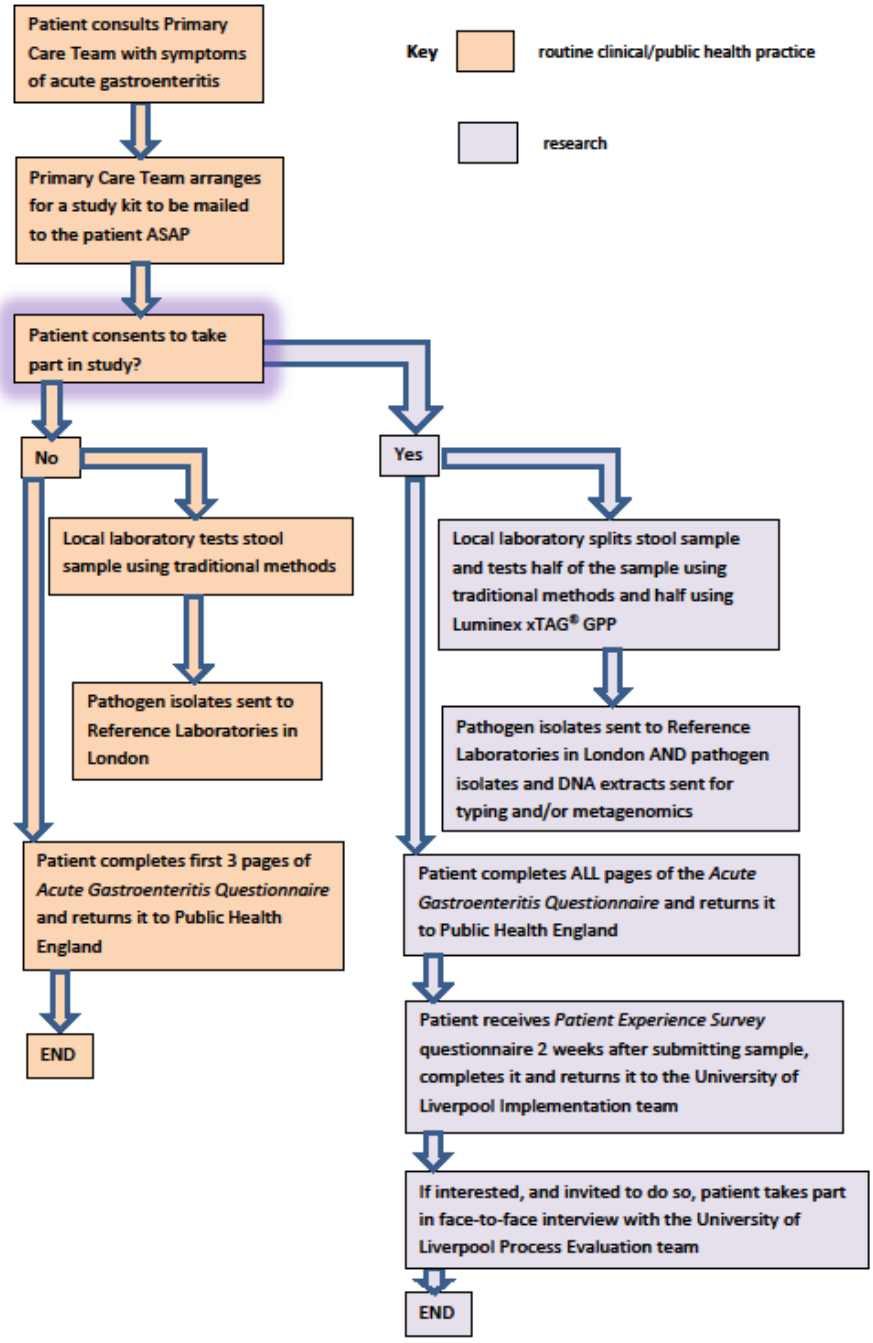
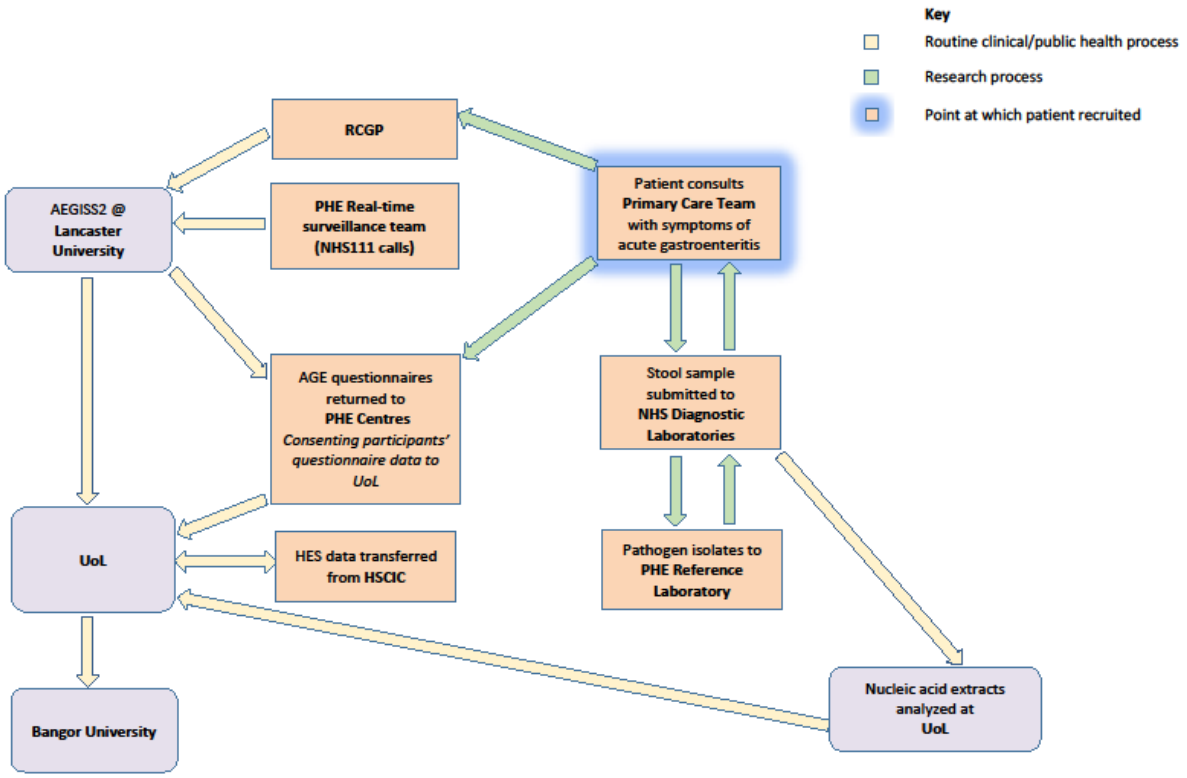


Figure 2. Post patient recruitment data flow for the INTEGRATE project. AEGISS: Ascertainment and Enhancement of Gastrointestinal Surveillance and Statistics; AGE: Public Health Acute Gastroenteritis; HES: Hospital Episode Statistics; HSCIC: Health and Social Care Information Centre; NHS: National Health Service; PHE: Public Health England; RCGP: Royal College of General Practitioners; UoL: University of Liverpool.



Public Health Acute Gastroenteritis Questionnaires

Public Health Acute Gastroenteritis (AGE) questionnaires will be returned to PHE's health protection teams using reply-paid envelopes. These questionnaires contain the routine follow-up information that is collected and collated by the PHE to assist outbreak detection or investigation. In addition, these questionnaires will contain questions on quality of life during the acute illness. Quality of life will be measured using the EuroQol-5D-3L [6], which is the gold standard tool. This gives snapshots of quality of life at points in time. At this time point (time point 1), we will capture the quality of life during the acute illness.

Resource Use and Costs

Resource use and costs will be assessed from several different perspectives, described below, including the public sector and patients.

Public Sector, Including National Health Service and Social Services

Consistent with National Institute for Health and Care Excellence's (NICE) methods for the development of public health guidance, we will adopt a public sector costing perspective. Although productivity costs are not routinely included in analyses, we will collect the data for consideration in sensitivity analysis. Unit costs will be derived from standard sources such as the Personal Social Services Research Unit Costs of Health and Social Care, the British National Formulary for drug costs, and NHS reference costs. The costs of laboratory and public health services will be obtained from PHE.

Patients

Patients who indicate in their consent form that they are willing to be contacted about a Patient Experience Survey (PES) will receive a questionnaire that seeks information about resource use 2 weeks after returning their stool sample pot. Most patients will have recovered fully 2 weeks later, and therefore, a complete picture of the costs they incurred because of their illness should be available. The short resource use questionnaires will capture details about the use of health care services, personal social services, days absent from work or school, and other potential costs. Quality of life, using EuroQol-5D-3L, will be assessed during the acute episode (time point 1) and at 2 weeks post recovery (time point 2). It will be used to calculate quality-adjusted life-years (QALYs).

Hospital Episode Statistics

Patients' use of secondary care services will be assessed by accessing Hospital Episode Statistics data sourced from NHS Digital. This will require a bespoke download, matching patients who have consented according to their NHS number, name, and date of birth, following a standard operating procedure to ensure patient anonymity and data protection.

Costs of Technology

These will include setup costs, including capital costs, the marginal costs of delivering the service, and the cost implications for patients using the NHS services. These costs will be obtained from Luminex and from time and motion studies conducted at participating microbiology laboratories.

Patient Experience Survey

The purpose of this survey is to explore service users' and, where relevant, their caregivers' perceptions and experiences of accessing the INTEGRATE service. Questions contained within the PES were developed from themes identified from the extant literature and include (1) motivations for accessing health care in relation to diarrhea; (2) predisposing or enabling motivations for accessing a given health care service; (3) experience and perceptions including the acceptability of self-stool sampling; and (4) dimensions of patient satisfaction, including, for example, communication and clarity of information.

Members of the public eligible to participate in the survey will be either a patient (aged ≥16 years) who has recently suffered from diarrhea and provided a stool sample, or a person who has parental, guardian, or caregiver responsibility for, and who will act as a proxy on behalf of, a patient who has recently suffered from diarrhea and provided a stool sample.

There was no upper age limit for sampling patients. However, where the patient is a minor (aged <16 years), the parent, guardian, or caregiver will be invited to respond on their behalf (as a proxy). We estimate approximately 5000 members of the public will be eligible to take part in the survey within a time frame of 15 months. During this period, all eligible participants will be consecutively recruited to participate in the survey as a means to achieving maximum variation in clinical and sociodemographic characteristics and to facilitate comparison across key purposive sampling criteria [7]. Participants will be invited to complete the questionnaire 2 weeks after returning their stool self-sample pot, allowing a 3-week recall period from the date of contact with the NHS.

Survey Distribution

When a member of the public contacts a collaborating GP, they will receive information in their study pack about the patient experience survey. If they express an interest in finding out more about this survey, they will be asked to identify a preferred contact route by either receiving a self-completion questionnaire through the post or accessing a Web-based self-completion questionnaire.

If prospective participants choose to receive this information through the post, they will be sent a public survey information pack containing an introductory letter, an information sheet explaining the aims of the study and the processes involved in participating in the survey, a copy of the self-completion questionnaire, and a prepaid return envelope addressed to the Project Office at the University of Liverpool. If prospective participants prefer to access these details online, they will receive an email. The email will include an electronic link to a secure, Web-enabled system containing a study introduction page. If interested, prospective participants can then access 2 further links. The first link will open an information page, which will outline the aims of the study and processes involved in participating in the online survey. The second link will enable prospective participants to access and complete the electronic version of the self-completion questionnaire (through the PHE Select Survey facility [8]).

Participants will be given 2 weeks to complete and return/submit their questionnaire. Nonresponders will be prompted (through their preferred route) with 1 follow-up reminder. These will include, as appropriate, a follow-up letter containing a further copy of the questionnaire and a prepaid return envelope or a follow-up email with an electronic link to the online questionnaire. The use of reminders is generally endorsed in texts on survey methods [9].

Summary of Outcome Measures

The outcome measures to be quantified within the research project are summarized in Table 1.

Plan of Analyses

Anomaly Detection

The underlying statistical model for human case incidence will be a spatiotemporal Cox process [10] in which the rate of calls at location x and time t is modeled as $\rho(x,t)=\lambda(x)\mu(t)R(x,t)$, where $\lambda(x)$ and $\mu(t)$ describe the normal patterns of variation in the spatial and temporal dimensions, respectively, of the call rate, thereby taking account of the geographical distribution of the user population, seasonal variation in disease risk, and reporting artifacts such as day-of-the-week effects. The term $R(x,t)$ is a stochastic process with expected value 1 and represents unforeseen, spatially and temporally localized variations in the underlying disease risk.

Model parameters will be estimated by likelihood-based methods and fed into algorithms that update the predictive distribution of the *unexpected* component $R(x,t)$ automatically on receipt of each day's incident call data. Results will be posted overnight in the form of maps showing localities, if any, where the data indicate a high probability that the current value of $R(x,t)$ exceeds a specified threshold.

System Performance

The performance of the new surveillance system compared with routine sampling will be assessed by analyzing the outcome-based indicators and comparing time with detection, decision to act, and the size of outbreaks described using both traditional and new diagnostic systems (range, mean, and median number of cases), outbreak settings, modes of transmission identified, and vehicles identified. Each critical time point along the diagnostic and detection pathway from symptom onset to diagnosis and detection of a cluster or outbreak will be examined.

Table 1. Resource use and costs outcome measures to be quantified within the research program.

Outcome measures	How to measure
Resource use and costs outcome measures	
Use of health care services	Resource use questionnaire (PES[a]) to patients
Use of personal social services	Resource use questionnaire (PES) to patients
Days absent from work or education	Resource use questionnaire (PES) to patients
Other potential cost impacts	Resource use questionnaire (PES) to patients
Use of secondary care services	Hospital Episode Statistics from NHS[b] Digital
Costs of technology	Interviews with Luminex (new technology) and time and motion studies at microbiology laboratories (existing technology)
Health outcome	EQ-5D-3L[c] questionnaire administered at 2 time points: time point 1, during the acute illness; and time point 2, 2 weeks after return of the Acute Gastroenteritis Questionnaire
System outcome measures[d]	
Time to detection of event	Laboratory records, date of AEGISS[e] anomaly detection, date that Consultants in Communicable Disease Control initiate an investigation
Compliance with sampling among people with symptoms	Laboratory records (number of samples requested) and GP[f] records (number of samples submitted)
Time to detection of a positive result	Laboratory records
Numbers of false-positive and false-negative stool samples	Laboratory records
Positive predictive value	Calculated from laboratory records using the formula: Σ true positives/Σ test outcome positives (ie, true positives + false positives)
Diagnostic gap	Laboratory records: percentage of negative samples using either system
Size of outbreaks detected	Outbreak investigation reports: range, mean, and median numbers of cases

[a]PES: Patient Experience Survey.

[b]NHS: National Health Service.

[c]EQ-5D-3L: EuroQol-5D-3L descriptive system.

[d]These will be captured for traditional methods and new diagnostic technology.

[e]AEGISS: Ascertainment and Enhancement of Gastrointestinal Surveillance and Statistics.

[f]GP: general practitioner.

Economic Modeling

The model structure will be based on a decision analysis in which the alternative options will be specified according to treatment pathways and strategies for public health intervention. The impact and scale of outbreaks will be modeled using agent-based models in which hypothetical cohorts are subject to an instantaneous rate of infection, which varies depending on the proportion of the population who are infected. This approach has several advantages over the traditional health economic models, which are restrictive in their predictive capabilities, and scenario testing. The model will be parameterized with point estimates and associated variances, derived from a purposive review of the published literature, from routinely collected data from PHE (both historical and contemporary), and from data generated during the research. These will include parameters relating to host-pathogen interactions; rate parameters that define the transition of patients among relevant states (eg, susceptible, diseased, and symptomatic and/or infectious); test characteristics, defined by sensitivity, specificity, and positive and negative predictive values; costs (associated with screening, patients' use of NHS community, primary and secondary care services, treatments, and other investigations); and health outcomes (defined by health state utilities based on UK tariff scores assigned to each model state and mortality estimates).

Calculating and Judging Cost-Effectiveness

Expected costs and benefits will be estimated to calculate incremental cost-utility ratios (costs per QALY gained) for a range of scenarios, specified by infection type, clinical course, and public health response. Estimates of the incremental cost-effectiveness ratios (ICERs) will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness set by NICE, and a range of one-way sensitivity analyses will be conducted to assess the robustness of the analysis. These will be presented as a Tornado plot. Multivariate sensitivity analyses will be applied where interaction effects are suspected. The joint uncertainty in all parameter estimates will be propagated through the model by use of probabilistic sensitivity analysis and construction of cost-effectiveness acceptability curves that present the probability of clinical strategies being

cost-effective, conditional on the chosen threshold for cost-effectiveness (representing the marginal value of health). Scenario analyses representing, for example, changes in service configuration will be conducted to estimate a range of ICERs for different circumstances.

Ethics

For the human case data, ethics permissions and approvals have been obtained from the following:

- National Research Ethics Service, REC reference: 15/NW/0233
- NHS Health Research Authority Confidential Advisory Group (CAG), CAG reference: 15/CAG/0131
- The Information Governance Toolkit, Department of Health and Social Care hosted by the Health and Social Care Information Centre (now NHS Digital), UoL reference: 8HN20, Lancaster University reference: EE133831-HAM-EAOPOCR
- NHS Research Management and Governance Committees, IRAS number: 173789
- University of Liverpool Ethics Sub-Committees, reference: UoL001111
- Honorary NHS contracts, research passports, and letters of access have been obtained for research staff working on the project as necessary.

Results

The project commenced on April 1, 2013. Favorable approval was obtained from the Research Ethics Committee on June 15, 2015, and the first patient was recruited on October 13, 2015, with 1407 patients recruited and samples processed using traditional laboratory techniques as of March 2017.

Discussion

This study investigates whether modern microbiological methods can be used to improve surveillance for GI disease while also examining the costs and limitations associated with the enhanced system. It compares the results obtained using traditional laboratory techniques with those obtained using modern sensitive molecular and genomic microbiology techniques. The strength of the study is the collaboration between lead public health partners and researchers in this field. However, there are a number of challenges in this study. For example, the plans for work are based on the assumption that implementation of the surveillance streams and their providers will continue in their current form for at least the period of study recruitment. Ethical permissions are granted under this proviso, but as with the provision of all health services, changes can occur rapidly. If there are changes to the study protocol, then these must be reflected in amendments to the ethics agreements, and the research governance including confidentiality agreements required for this to happen can take a significant amount of time to go through the review process, delaying the progression of data collection. Another challenge is that of recruiting a sufficiently large number of patients for analysis, to allow reasonable comparison of the results of the traditional and modern microbiological testing. This is particularly true, given that GPs often do not encourage patients to provide a stool sample unless they have had clinical GI symptoms for an extended period or unless they are in a high-risk group such as those who are young, old, or immunocompromised.

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The datasets generated during this study are not publicly available because of the issues of data confidentiality and patient identifiable information. Data are, however, available from the authors on reasonable request and with appropriate ethical permissions.

Conflicts of Interest

None declared.

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Abbreviations

APHA: Animal and Plant Health Agency
CAG: Confidential Advisory Group
GI: gastrointestinal
GP: general practitioner
HPRU: Health Protection Research Unit
ICER: incremental cost-effectiveness ratios
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
PCR: polymerase chain reaction
PHE: Public Health England
QALY: quality-adjusted life-year
RCGP RSC NMN: Royal College of General Practitioners' Research and Surveillance Centre National Monitoring Network
xTAG GPP: Luminex xTAG Gastrointestinal Pathogen Panel

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Protocol

Exploring Severe Mental Illness and Diabetes: Protocol for a Longitudinal, Observational, and Qualitative Mixed Methods Study

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Abstract

Background: The average life expectancy for people with a severe mental illness (SMI) such as schizophrenia or bipolar disorder is 15 to 20 years less than that for the population as a whole. Diabetes contributes significantly to this inequality, being 2 to 3 times more prevalent in people with SMI. Various risk factors have been implicated, including side effects of antipsychotic medication and unhealthy lifestyles, which often occur in the context of socioeconomic disadvantage and health care inequality. However, little is known about how these factors may interact to influence the risk of developing diabetes and poor diabetic outcomes, or how the organization and provision of health care may contribute.

Objective: This study aims to identify the determinants of diabetes and to explore variation in diabetes outcomes for people with SMI.

Methods: This study will employ a concurrent mixed methods design combining the interrogation of electronic primary care health records from the Clinical Practice Research Datalink (CPRD GOLD) with qualitative interviews with adults with SMI and diabetes, their relatives and friends, and health care staff. The study has been funded for 2 years, from September 2017 to September 2019, and data collection has recently ended.

Results: CPRD and linked health data will be used to explore the association of sociodemographics, illness, and health care–related factors with both the development and outcomes of type 2 diabetes in people with SMI. Experiences of managing the comorbidity and accessing health care will be explored through qualitative interviews using topic guides informed by evidence synthesis and

expert consultation. Findings from both datasets will be merged to develop a more comprehensive understanding of diabetes risks, interventions, and outcomes for people with SMI. Findings will be translated into recommendations for interventions and services using co-design workshops.

Conclusions: Improving diabetes outcomes for people with SMI is a high-priority area nationally and globally. Understanding how risk factors combine to generate high prevalence of diabetes and poor diabetic outcomes for this population is a necessary first step in developing health care interventions to improve outcomes for people with diabetes and SMI.

Trial Registration: ClinicalTrials.gov NCT03534921; https://clinicaltrials.gov/ct2/show/NCT03534921

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KEYWORDS

schizophrenia; bipolar disorder; diabetes mellitus; diabetes complications

Introduction

Background

Severe mental illness (SMI) refers to a set of disabling conditions such as schizophrenia, schizoaffective disorder, or bipolar disorder. People with SMI, who account for around 1% of the population [1], may experience feelings of persecution, hallucinations, problems with mood, impaired cognition, and lack of motivation. These difficulties can have an adverse impact on several areas of life such as housing, employment, relationships, and personal care, which can, in turn, increase the likelihood of mental and physical health problems. They have a reduced life expectancy, living for 15 to 20 years less than the population as a whole, and experience poorer health outcomes [2-5].

Diabetes is a significant contributor to the increased morbidity and mortality experienced by people with SMI. The condition is 2 to 3 times more prevalent in this population [6-8], and complications of diabetes are higher than for people without SMI [9,10]. The link between the metabolic side-effects of antipsychotic medication and diabetes has been well-documented [11-13], but there are additional complexities; other work points to the possibility of a genetic neuroinflammatory mechanism predisposing people toward both conditions [14], which could explain the occurrence of the comorbidity independent of antipsychotic medication [15,16]. Furthermore, other factors have been implicated such as lifestyle health risk factors such as diet [17], smoking [18,19], low levels of physical activity [20], and higher levels of other comorbid conditions [21]. However, little is known about the relative contribution of these factors, or about possible synergistic relationships that may increase the risk of people with SMI developing diabetes or experiencing poorer diabetes outcomes.

There is strong evidence that people with SMI are more likely to be socially disadvantaged than people without SMI [22-24], experiencing reduced access to material, financial, social, or structural resources such as transport, childcare, paid leave, and advocacy services [25]. Accordingly, people with SMI have difficulty navigating health care systems, less capacity to take advantage of health promotion opportunities, and encounter more barriers to taking up interventions designed to prevent or treat illness. Moreover, despite calls for integrated service models that treat the *whole person* [26], such models of service delivery can be thwarted by rigid boundaries between primary and secondary care, unclear practitioner accountability for mental and physical health care [27,28], and diagnostic overshadowing (misattributing physical health problems to mental illness) [29].

There is conflicting evidence about the quality of diabetes care for those with and without SMI [10,30-34]. In addition, little is known about the costs of diabetes screening, monitoring, and management for this group, or about the relationship between diabetes interventions and health outcomes. Furthermore, although a recent study demonstrated that diabetes distress—the emotional burden of managing a serious, chronic condition—is known to significantly affect people with diabetes who do not have SMI [35], there is limited evidence on how diabetes might impact upon the mental health of people who already experience psychological vulnerabilities.

Improving diabetes care for people with SMI is a high priority nationally and globally [36,37]. Understanding how SMI and other risk factors combine to generate high diabetes prevalence and poor diabetes outcomes and how the quality and quantity of health care services and interventions can impact on these risk factors is a necessary first step in developing health care interventions to improve outcomes for people with diabetes and SMI.

Objectives

This study aims to identify the determinants of diabetes in people with SMI and to explore variation in diabetes outcomes for people with SMI to develop potential health care interventions that can be tested further.

The study has the following objectives:

1. In people with SMI, to identify which sociodemographic, illness, family history, and lifestyle factors are associated with the development of diabetes
2. In people with SMI and diabetes, to identify which sociodemographic, illness, family history, and lifestyle factors are associated with variation in diabetes and mental health outcomes
3. In people with SMI, to compare health care interventions, physical and mental health outcomes in those with diabetes, and those without diabetes
4. In people with diabetes, to compare health care interventions, physical and mental health outcomes in those with SMI, and those without SMI

5. To understand the factors that influence access to, and receipt of, diabetes care for people with SMI and explore the experience of diabetes health care by people with SMI
6. To compare diabetes care provision for people with and without SMI, and estimate costs for these
7. To identify which health care interventions (eg, medication, referrals, and care pathways) may be associated with better diabetes outcomes for people with SMI and diabetes.

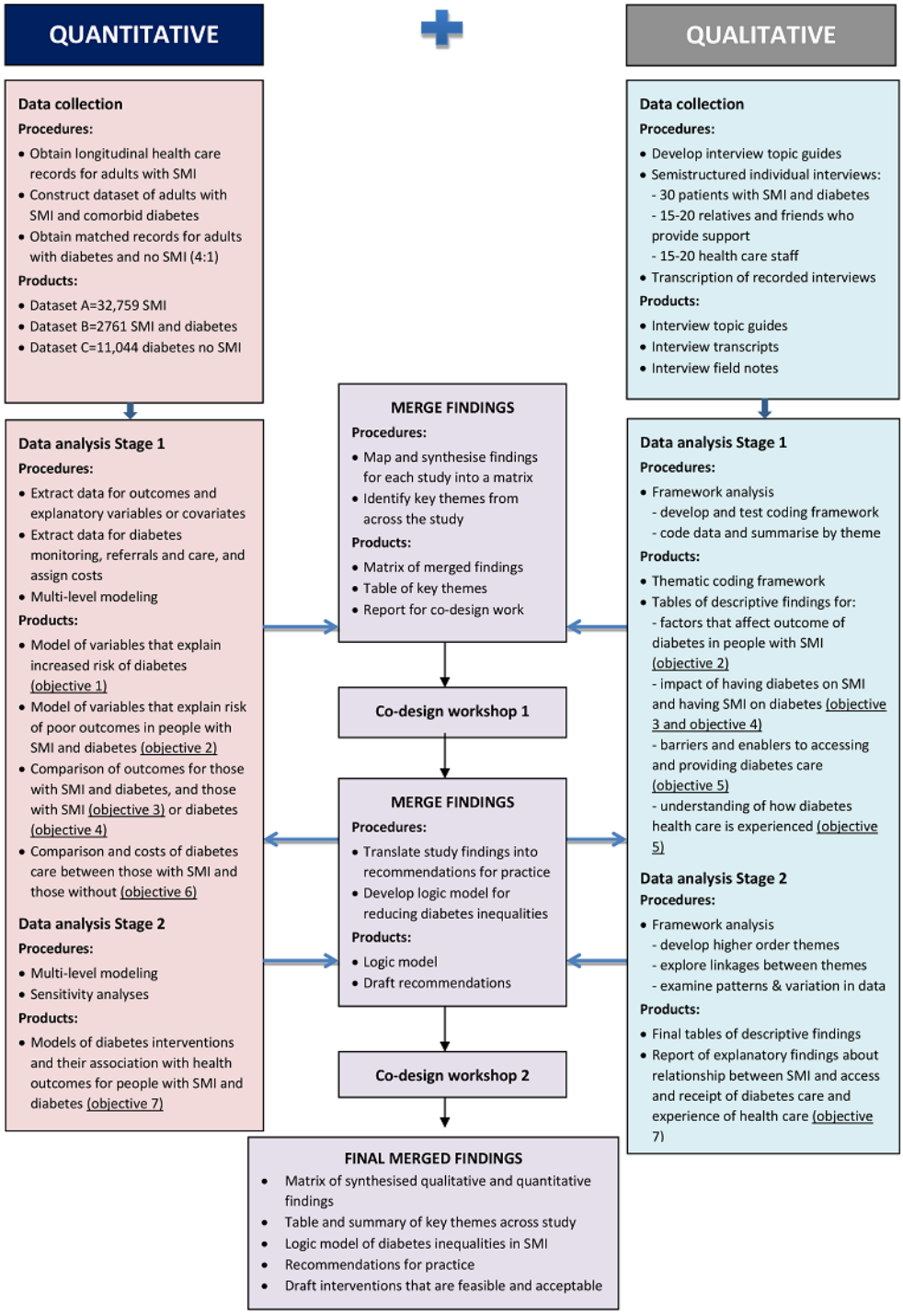
Methods

Design

The underpinning theoretical framework for the study conceptualizes socioeconomic conditions as a fundamental cause of health inequalities [25]. Under a social inequalities framework, a concurrent triangulation mixed methods design will be used comprising (1) a quantitative longitudinal observational study of anonymized individual patient records of adults diagnosed with SMI in Clinical Practice Research Datalink (CPRD) and (2) a qualitative interview study of people with coexisting SMI and diabetes, their family or friends, and health care staff involved in diabetes and mental health care. Both workstreams will be informed by a synthesis of existing evidence.

The mixed methods design is underpinned by a pragmatic paradigm, which acknowledges that data types, when integrated together, will enable the development of a more complete understanding of health inequalities in this population than would be possible from either method alone [38]. Interrogation of quantitative data from CPRD will be used to generate insights into inequalities through identifying trends, patterns, and correlations, indicating which groups are more at risk of developing diabetes or experiencing poor diabetes outcomes. These data will be complemented by findings from the analysis of qualitative interviews conducted to explore the difficulties people with SMI have in managing their diabetes and accessing services. The quantitative and qualitative data will be integrated iteratively as the study progresses; key findings emerging from the CPRD analysis will be explored further in interviews, and qualitative themes will be used to inform the choice of variables that can be explored in the quantitative dataset (see Figure 1). Key to both the quantitative and qualitative analyses will be exploring the effects of disadvantage and deprivation on risks, outcomes, and experiences for people with SMI and diabetes.

Figure 1. Study Flow Diagram.



Patient and Public Involvement

The study is supported by DIAMONDS VOICE, a patient and public involvement (PPI) panel that contributes to a wider research program called Diabetes and Mental Illness: Improving Outcomes and Services. The panel was involved in prioritizing the research questions during the design phase of this study and reviewed all patient and public-facing documentation before submission to the National Health Service Research Ethics Committee. The panel will continue to contribute to the study in the following ways: advising on how to ask sensitive questions, acting as practice interviewees, advising on minimizing participant burden, promoting the study at local events, and advising on recruitment and dissemination strategies. Both the project management team and the study steering committee have service user representation to ensure that the patient perspective is incorporated in project decisions.

Ethical Approval and Data Use Agreement

A data use agreement for CPRD records and linked Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data was granted by the International Scientific Advisory Committee (ref: 17_161R). Approvals for the qualitative study were granted by the National Institute of Health Research Health Research Authority and the Greater Manchester West Research Ethics Committee (ref: 18/NW/0005), following a submission made through the Integrated Research Application System (ref: 235328).

The study is registered on the NIHR Central Portfolio Management System (CPMS; ref: #37024) and ClinicalTrials.gov (record identifier #NCT03534921).

Quantitative, Longitudinal, and Observational Study

This workstream examines the impact of potential risk factors on the development and the time to onset of diabetes in people with SMI and variation in mental and physical health outcomes in people with comorbid SMI and diabetes. Diabetes health care and outcomes for people with SMI and diabetes will be compared with outcomes for people with either condition alone. Variations in diabetes screening, monitoring, and management will be examined and costs estimated. The role of these interventions in contributing to health outcomes will be explored.

Study Population

The primary study population comprises adult patients (age ≥18 years) living in England who are registered with a general practice contributing up to research standard data to CPRD and who have remained within CPRD for the study period, from April 1, 2000, to March 31, 2016.

Datasets

CPRD is the world's largest computerized database of anonymized longitudinal medical records from primary care. Information includes records of symptoms, diagnoses, referrals, prescriptions issued in primary care, records of immunizations and vaccinations, laboratory test results, lifestyle information (eg smoking and alcohol status), and all other types of care administered as part of routine general practice. Currently, data are collected on over 5 million active patients from 674 general practices, covering around 6.9% of the UK population registered with a general practitioner [39].

Records for 3 population groups will be extracted from CPRD. The datasets will be structured as shown in Table 1.

Data Linkages

Electronically linked data for individuals in the study population will be obtained from the following sources: HES data for hospital admissions [41], ONS for dates and causes of death [42], and the Index of Multiple Deprivation (IMD) for area deprivation at practice and patient level [43].

Health and Health Care Outcomes

The following outcomes listed in Table 2, corresponding to the objectives described above, will be examined.

Analyses may be limited by the quality and availability of data for some of the above variables, but wherever possible, validated code lists will be employed.

Table 1. Structure of the Clinical Practice Research Datalink datasets.

Dataset	Population	Specification	Estimated sample size of patients
Dataset A	Adults (≥18 years) with SMI[a]	Longitudinal health care records of adult patients with SMI defined as the presence of a clinical diagnostic code for schizophrenia, affective disorder (divided into bipolar or unspecified affective disorder), and other types of psychoses. Read codes previously tested and applied by the research team [37] will be used to identify the presence of SMI.	33,000
Dataset B (a subset of dataset A)	Adults with a diagnosis of SMI and diabetes mellitus	Diabetes, identified using previously tested and validated Read codes, will be further defined as the presence of a clinical diagnostic code for type 1 diabetes, type 2 diabetes, drug-induced diabetes, or unspecified diabetes. Individuals with a diagnostic code of gestational diabetes, cystic fibrosis, and hemochromatosis will be excluded.	3600 based on a predicted diabetes prevalence of 11.1% [40]
Dataset C (matched controls to dataset B)	Adults with a diagnosis of type 2 diabetes but without SMI	Patients with type 2 diabetes in dataset B will be matched by Clinical Practice Research Datalink to a cohort of patients who have a diagnosis of type 2 diabetes but without SMI (controls) with a case to control ratio of 1:4 on the basis of age, gender, and practice.	14,400

[a]SMI: severe mental illness.

Table 2. Health and health care outcomes corresponding to objectives.

Outcome	Objective #
Diabetes status and onset	1
Diabetic and cardiovascular control (measured by recorded hemoglobin A_{1c}, blood pressure, and cholesterol levels)	2
Diabetic complications: acute hyperglycemic events, hypoglycemia, microvascular complications (retinopathy, neuropathy, and nephropathy)	2, 4
Diabetic complications: macrovascular complications (coronary artery disease, cerebrovascular disease, and peripheral arterial disease)	2, 3, 4, 7
Hospital admissions for the above conditions	2, 3, 4, 7
Mental health outcomes including severe mental illness relapses (measured by hospital admissions and general practitioner referrals to community mental health teams or crisis teams) and markers of depression or anxiety (ie, general practitioner diagnoses or prescriptions for antidepressants)	2, 3, 4, 7
Mortality	2, 3, 4, 7
Health care utilization (including the number and type of primary care consultations) and costs	6
Health care interventions (eg, first and second generation antipsychotic and antidiabetic medications, care pathways, and referrals)	6, 7

Risk Factors and Explanatory Variables

Known risk factors and covariates for developing diabetes and diabetes complications will be included in the analyses to determine their relative association with the development and progress of diabetes in people with SMI. The list of factors will be determined by evidence synthesis, complemented by expert consensus, and will be responsive to emerging findings from the qualitative interviews.

The candidate risk factors include patient demographics and socioeconomic markers (sex, age, ethnic group, area deprivation, and rurality), lifestyle (obesity, smoking, and alcohol consumption), social vulnerability markers such as housing status, hyperlipidemia, family history, type of SMI and diabetes (including order and timing of diagnosis), length of diagnosis, illness severity, and multimorbidity.

Statistical Analysis

It is anticipated that there will be around 5 to 6 years of data on each individual, which will enable more robust analyses than cross-sectional data would permit. Longitudinal data afford better control for unobserved characteristics, at either the individual or practice level that plausibly impact both practice performance and patient outcomes (eg, practice style and culture), and which may otherwise confound important relationships. In addition, repeated observations at practice or patient level allow the investigation of lags in the relationship between diabetes management and outcomes, as the timing of events can be observed. Both these factors are crucial in identifying plausible causal mechanisms linking diabetes management to outcomes.

The potential for confounding will be addressed by matching on index date to avoid inclusion of *ghost* patients, conducting sensitivity analyses, and evaluating the potential for unmeasured confounding and the size of any observed effects.

A range of regression models will be used for statistical analyses, taking account of the hierarchical structure of the data, where, for example, activities are *nested within* patients who in turn are nested within practices. Linear, logistic and survival regressions will be applied as appropriate depending on the outcome variable of interest. Multilevel mixed effects will be estimated to account for the correlation in the longitudinal health records of the same patient, as well as the unobserved correlation at practice level. An outline of planned analyses by study objective is given in Table 3.

Under all objectives, analyses will be conducted in line with the inequalities framework to quantify the absolute and relative effect of social inequalities on quality of care and outcomes. Under objectives 1 and 3, the disparities will be modeled within the SMI population, under objective 2 within the SMI and diabetes population, and both within and between the diabetes populations (SMI and non-SMI) under objectives 4 to 7. Specifically, where sample size permits, analyses will be stratified, for example, by ethnicity and or deprivation and disadvantage markers such as IMD; housing status and rurality will be used as independent variables to estimate gap or gradient effects.

All statistical models will include a set of relevant patient, local population, and practice covariates where possible to control for confounding and interacting influences potentially masking the relationship between diabetes management and outcomes.

In sensitivity analyses, noncompliance (including refusal of treatment, informed dissent, and nonattendance) will be included as an independent variable in the models. Sensitivity analyses will be conducted with noncompliance treated as either a time-dependent (*expiring*) or time-independent (*nonexpiring*) variable and as specific to the refused treatment or as a general marker of noncompliance. Noncompliance will be used to create *offer of treatment* explanatory variables, facilitating *intention-to-treat* type analyses.

Robustness checks will be carried out to ensure our results are reliable, and plausibility tests to ensure findings are meaningful in practice and can inform policy. Model assumptions will be checked for all analyses, and if they are in doubt, the data will be transformed before analysis or alternative nonparametric analysis methods will be used.

Table 3. Summary of statistical analysis plan by study objective.

Objective #[a]	Description	Datasets	Variables	Analysis
1	The impact of key explanatory variables on both diabetes status and time to onset of diabetes	Quantitative dataset A (people with SMI[b])	Explanatory variables: sociodemographic characteristics, medication use, physical and mental health status, family history of diabetes, biometric data dysregulation, and lifestyle factors	Multilevel modeling: logistic model (diabetes status) and survival model (time to diabetes onset)
2	The impact of key explanatory variables (as above) on diabetes and mental health outcomes	Quantitative dataset B (people with SMI and type 2 diabetes)	Outcomes: diabetic and cardiovascular control; diabetic complications; hospital admissions; mental health outcomes, for example relapses and episodes of depression and anxiety and mortality	Repeated measures mixed models: linear, logistic, and survival models
3	The impact of diabetes status and other explanatory variables (as above) on physical and mental health outcomes	Quantitative dataset A	Outcomes: macrovascular diabetic complications, hospital admissions, mental health outcomes, and mortality	Poisson or negative binomial multilevel models for count outcomes, logistic multilevel models for binary outcomes
4	The impact of SMI status and other explanatory variables (as above) on physical and mental health outcomes	Quantitative datasets B and C (matched cohort of non-SMI patients with diabetes)	Outcomes as above	Similar multilevel modeling to objective 3
6	Comparison of, and cost estimation for, diabetes health care provision for people with and without SMI	Quantitative datasets B and C	Contacts with primary care staff and hospitalization but not medication costs: Health care costs will be calculated by attaching unit costs to contacts recorded in the Clinical Practice Research Datalink database and also hospital inpatient episodes, from the linked Hospital Episode Statistics data. National average costs will be calculated using National Health Service Reference Costs and Personal Social Services Research Unit costs.	Cost data will be modeled on patient level as a nonlinear function (such as exponential) of covariates to take into account the nonnegative, highly skewed, and leptokurtic characteristics. We will choose the model depending on the distribution of the cost data. Random intercepts will be estimated to capture the baseline differences in health care provision at practice level.
7	Impact of SMI status and other explanatory variables (as above) on whether or not someone receives a diabetes intervention	Quantitative datasets B and C	Diabetes interventions, for example, regular reviews, monitoring, referral to education programs, foot checks, retinopathy screening, and referrals to secondary care. Outcomes, for example, diabetes admissions and diabetic complications	The probability of receiving interventions will be modeled as a function of SMI status, patient characteristics, and other key predictors. Random intercepts at practice level will be included in the model to capture the systematic differences in service provision.

[a]Objective number 5 will be explored in the qualitative workstream.

[b]SMI: severe mental illness.

Qualitative Interview Study

Under the inequalities framework, the qualitative study aims to develop understandings of the factors that influence access to and receipt of diabetes care and how health care service provision is perceived by people living with SMI and diabetes, those who support them, and health care professionals. The interviews will be conducted in person or over the telephone, using topic guides that have been informed by expert consultation, existing literature, and preliminary CPRD analyses.

Population

Study participants will include (1) adults with SMI and diabetes (excluding gestational diabetes) living in the community (n=30-50), (2) relatives or friends who are involved in the care of a person with SMI and diabetes (n=15-20), and (3) health care staff (commissioners, clinicians, nurses, and other health care staff who are involved in health care services for people with SMI and diabetes; n=15-20).

Sampling

People with SMI and diabetes will be included in the study if they are:

- Aged 18 years or older
- Diagnosed with a SMI and not currently experiencing an acute relapse
- Have a diagnosis of diabetes (excluding gestational diabetes)
- Live in the community
- Have capacity to consent to the study.

Maximum variation purposive sampling will be used, informed by demographic and illness characteristics identified during the descriptive analysis of CPRD data and the social inequalities theoretical framework to gain understandings of the diversity of experience in this group. People with SMI and diabetes will be sampled from rural and urban areas, areas of wealth and deprivation, and areas with diverse communities.

To ensure representation from different health care disciplines, health care staff will be sampled purposively. GPs, practice nurses, diabetes nurses, mental health nurses, case managers, psychiatrists, and diabetologists will be invited to take part in the study.

The sampling strategy in all groups will be continually monitored as the study progresses to ensure that diversity of experience is captured. Recruitment will continue until data saturation is reached, that is, no new themes are emerging from the interviews [44].

Recruitment

Evidence suggests that around 20 to 30% of people with SMI are supported solely within primary care [45]. Therefore, to understand how people with SMI experience diabetes care, it is important to sample from both general practices and specialist mental health services. Patients and relatives will be identified by general practice and mental health service staff using database and caseload searches. Following screening by a clinician, eligible patients will be sent a study pack containing an invitation letter, a participant information sheet, a response form, and a prepaid return envelope.

Patients will also be recruited via existing research cohorts and clinic and website advertisements. Patients from existing cohorts who have agreed to be contacted for future research will receive a study pack. Patients or relatives who express an interest in participating after seeing an advertisement will also be provided with the pack. Patients who contact the study team will be asked to provide permission to access medical records to screen for eligibility.

To recruit relatives or friends to the study, participating patients will be asked to identify a person who supports them who will then be approached by the research team. Relatives who are known to clinicians will also be provided with a study pack.

For health care staff recruitment, lead clinicians in participating general practices and mental health services will be asked to identify health care staff with experience of providing services to this population.

Consent

Written or audio-recorded informed consent will be obtained from all participants. Study information will be provided (written and verbal) using materials that have been developed with the PPI Group. Capacity to participate will be assessed by staff with appropriate experience during contact telephone calls and again before interview.

Data Collection

All interviews will be conducted using semistructured topic guides (see Table 4), which will be informed by the evidence synthesis and consultation with the PPI Group and the project team. Data collection will begin in April 2018, and it is anticipated that it will be completed by the end of December 2018. The topic guide will be reshaped iteratively as the project progresses, being influenced by developing themes, CPRD analyses, and new evidence that emerges in the field.

Interviews will be conducted by an experienced qualitative researcher and will last for a maximum of 90 min (patients and relatives) or 45 min for health care staff. With participants' permission, interviews will be audio-recorded.

Table 4. Qualitative interview topics by participant group.

Participant group	Topic areas
Patients with severe mental illness and diabetes	• Emergence of the conditions and experience of diagnosis • Day-to-day experiences of living with the comorbidities including self-management and how morbidities impact one another • Experience of accessing and receiving health or other support services • Suggestions for improvements to services
Relatives and friends who provide support	• Experiences of providing support • The impact of the comorbidity on shared activities of daily life • Perceptions of support received from formal services for the person they care for and themselves • Perceptions of barriers and facilitators to accessing care • Suggestions for improvements to services
Health care staff	• Role in supporting people living with this comorbidity • Perceptions of the challenges faced by people living with the comorbidity • Perceptions of barriers and facilitators to integrating physical and mental health services • Perceptions of staff training needs • Suggestions for improvements to services

Data Analysis

Data will be analyzed using NVivo 11 (QSR International). The framework method [46] will be employed, which combines deductive analysis of a priori themes identified in the evidence synthesis, the quantitative analysis, and through expert consultation, with inductive analysis of themes that emerge from the data. Analysis comprises a 5-stage process of scaffolding (identifying and extracting themes), indexing (labeling and sorting data to test the framework), coding (coding the data to the framework), descriptive analysis (categorizing and classifying data into higher order themes), and explanatory analysis (detecting thematic patterns and relationships). Each group of participants will be analyzed separately before cross-group analyses will be undertaken to triangulate the qualitative data. Areas of convergence and divergence within and across the 3 groups of data will be explored, and possible explanations for contradictory findings will be proposed. To ensure dependability and credibility [47], the key steps of the analysis will be conducted by at least two researchers, and the framework will be reviewed regularly by the project team and PPI panel.

Results

The study was funded for 2 years, from September 2017 to September 2019. Data collection is ongoing in the qualitative workstream and is expected to be completed by the end of December 2018.

In the later stages of analysis, the findings from the qualitative study will be merged with quantitative analyses using established integration techniques such as comparison matrices to validate, confirm, or refute findings, and joint data displays [48]. These analyses will be used by the project team to create a logic model drawing on process evaluation methodology [49]. The model will delineate how diabetes contributes to health inequalities in people with SMI and diabetes, exploring the relationship between health care provision and inequalities. Analytic rigor will be assured through regular discussion of analytic strategies with the project team, study steering committee, and PPI group.

Findings will be considered in 2 multistakeholder workshops involving service users, family members, researchers, clinicians, commissioners, health service managers, and representatives from third sector organizations to develop recommendations to improve diabetes care for people with SMI. The first workshop will review the merged findings, identify further analyses that can be conducted, and will create draft recommendations to improve health care. The second workshop will use the final analyses to refine the draft recommendations and to design and assess the feasibility of interventions or care pathways where the need for these has been identified empirically.

A range of channels will be used to communicate study findings to participants, stakeholders, and likely beneficiaries of the research. Key audiences will include patients, family members, health care staff, policy makers, voluntary and commercial sector organizations, and researchers. Representatives from these sectors will be invited to a dissemination event at the end of the study.

Research outputs will take the form of written reports, journal articles, oral presentations, and content distributed through international, national, and local networks, websites, and social media.

Discussion

People with SMI face significant health inequalities compared with the population as a whole, experiencing poorer physical health and having a reduced life expectancy of 15 to 20 years. Diabetes contributes to this inequality, occurring 2 to 3 times more often in people with SMI. Although various sociodemographic, genetic, illness, and health care–related factors are thought to increase the risk of developing the condition, the relative influence of these factors, and how they might interrelate, remains poorly understood. Furthermore, evidence suggests that people with comorbid SMI and diabetes experience poorer diabetic outcomes than those without SMI.

This research will provide greater understandings of why people with SMI are more at risk of developing diabetes and why their diabetic outcomes may be poorer than those without SMI. Associations between diabetes screening, monitoring and management, and health outcomes will be investigated to identify interventions with the potential to improve outcomes in this population. In addition, exploring the health care needs and health care delivery concerns of people with comorbid SMI and diabetes, relatives or friends who support them, and health care staff will enable the development of a more comprehensive understanding of the factors that contribute to poor outcomes and the drivers of improved health outcomes in SMI and diabetes.

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Authors' Contributions

SB, JT, LH, SLP, and NS wrote the paper. DS, RJ, RIGH, JR, SG, CH, TD, and SA contributed to the conception and design of the study and the development of the original study protocol. All authors reviewed and approved the paper.

Conflicts of Interest

DS is expert advisor to the National Institute for Health and Clinical Excellence (NICE) center for guidelines and a member of the current NICE guideline development group for *Rehabilitation in Adults With Complex Psychosis and Related Severe Mental Health Conditions*, board member of the National Collaborating Centre for Mental Health, and clinical advisor (paid consultancy basis) to National Clinical Audit of Psychosis. CH and SG are members of the National Institute for Health Research Health Technology Assessment commissioning board. None of the other authors declared competing interests.

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Abbreviations

CPRD: Clinical Practice Research Datalink
HES: Hospital Episode Statistics
IMD: Index of Multiple Deprivation
ONS: Office for National Statistics
PPI: patient and public involvement
SMI: severe mental illness

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Protocol

A Web-Based Study of HIV Prevention in the Era of Pre-Exposure Prophylaxis Among Vulnerable HIV-Negative Gay and Bisexual Men, Transmen, and Transwomen Who Have Sex With Men: Protocol for an Observational Cohort Study

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Abstract

Background: Gay, bisexual, and other men who have sex with men continue to bear a large burden of the HIV epidemic in the United States and are among the only populations with increasing incidence in recent years.

Objective: The *Together 5000* (T5K) Study aimed to enroll a US-based, racially diverse sample of HIV-negative men, transmen, and transwomen who are not on pre-exposure prophylaxis (PrEP) into an observational cohort to inform the design, implementation, scale-up, and evaluation of HIV prevention programs.

Methods: We used internet-based strategies to enroll a large, racially diverse national sample of HIV-negative men, transmen, and transwomen aged 16 to 49 years at high risk of HIV acquisition via sexual networking apps. Study participants are contacted every 6 months (in between annual surveys) for a brief survey on HIV testing, HIV diagnosis, and PrEP use (ie, attempts to access, PrEP initiation, and PrEP discontinuation). Participants complete annual self-administered at-home HIV testing and Web-based surveys. Using baseline serologic data and self-reported HIV testing history, we reconstructed a cohort of persons who were HIV negative at 12 months before baseline to estimate HIV incidence leading up to cohort enrollment.

Results: The study sample included 8777 participants from all 50 US states, Puerto Rico, and Guam; 50.91% (4468/8777) were persons of color and 25.30% (2221/8777) were young individuals aged 16 to 24 years. Per eligibility criteria, all T5K participants reported having sex with >2 male partners in the 90 days before enrollment, self-reported not having been diagnosed with HIV, and were not actively taking PrEP. In addition, 79.39% (6968/8777) reported >2 insertive condomless anal sex (CAS) acts, 61.02% (5356/8777) reported >1 receptive CAS acts in the past 90 days. Furthermore, most (7525/8777, 85.74%) reported never having taken PrEP. In total, 70.25% (6166/8777) were sent a self-administered at-home HIV test kit and 82.29% (5074/6166) of those sent a kit returned a sample for testing. The HIV incidence rate during the 12-month period leading up to enrollment was estimated to be 2.41 (95% CI 2.02-2.90) per 100 person-years.

Conclusions: A large, national, and racially diverse fully Web-based cohort of HIV-negative men, transmen, and transwomen at high risk for HIV seroconversion has successfully been recruited into longitudinal follow-up. This cohort is at high risk for HIV acquisition and can provide important insights related to the real-world uptake, impact, and equity of HIV prevention interventions in the United States. Participants can be invited to participate in trials aimed at testing strategies to improve the uptake of and engagement in these interventions.

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KEYWORDS

HIV; pre-exposure prophylaxis; implementation science

Introduction

Gay, bisexual, and other men who have sex with men (GBM) continue to bear the burden of the HIV epidemic in the United States and are among the only populations with increasing incidence in recent years [1]. The high rate of HIV incidence among GBM in the United States and the unabated racial and ethnic disparities in the era of HIV pre-exposure prophylaxis (PrEP) highlight the urgent need to understand more about PrEP uptake and missed prevention opportunities and their drivers [2]. Presently, PrEP is recommended by the Centers for Disease Control and Prevention [3,4] to prevent new HIV infections and has been supported by local health departments in many major US cities [5,6]. However, optimal implementation and delivery strategies that provide greater access to those in need of biomedical HIV prevention interventions have not been identified and may vary substantially by population, setting, and policy environment. Recent data suggest that, despite accounting for nearly half of all US HIV infections, black men represent fewer than 10% of those taking PrEP. In contrast, white men made up 27% of those infected with HIV in 2014 but accounted for 75% of those taking PrEP in 2015 [7].

Most data on PrEP uptake are based on insurance claims or pharmacy prescriptions for emtricitabine and tenofovir disoproxil fumarate. A major limitation of available insurance plan–based or even population-based data on PrEP uptake [8] is that they do not provide epidemiological or behavioral information on the underlying population of persons in *need* of PrEP. Thus, there is limited ability to assess both PrEP coverage and the major barriers and facilitators of PrEP uptake among those at the highest risk for HIV acquisition. Importantly, many individuals who are most in need of PrEP may not have regular encounters with or access to health care and thus may not be reachable via health care providers or other conventional provider-based intervention targeting strategies. Specifically, the most common way that US GBM meet sexual partners is via the internet, with a rapid and recent shift to the use of geosocial sexual networking mobile apps, making these platforms particularly important both for understanding barriers to PrEP uptake and targeting interventions [9-11]. We describe the protocol and baseline participant characteristics for the *Together 5000* (T5K) cohort study.

In response to a 2016 request for applications from the US National Institutes of Health (NIH) [12], we sought to recruit, via sexual networking apps, a racially and geographically diverse sample of HIV-negative men, transmen, and transwomen who have sex with men who are not on PrEP to better inform the design, implementation, scale-up, and evaluation of HIV prevention programs.

Methods

Target Population

The T5K cohort study used established ([13]; also CG et al, unpublished data, 2019) internet-based strategies to enroll a large sample of HIV-negative men, transmen, and transwomen who have sex with men aged 16 to 49 years and are at high risk of HIV acquisition. The cohort will be followed prospectively for 48 months for the outcomes of PrEP uptake and HIV seroconversion. We aimed to enroll a cohort of participants at high risk for HIV that was geographically diverse (ie, representing every US state and territory), racially and ethnically diverse (4468/8777, 50.91% participants of color), and young (2221/8777, 25.30% aged 16-24 years). We achieved these goals without needing to employ stratified sampling.

Cohort Eligibility and Recruitment

Open enrollment for T5K began in October 2017 and concluded in June 2018, when 67,166 of the estimated 649,000 (67,166/649,000, 10.35%) males eligible for PrEP across the United States were using it [8]. Participants were recruited via ads on men-for-men geosocial sexual networking mobile phone apps (Figure 1). Although not the targeted audience, transgender women and men were not excluded if they reported sex with men and otherwise met the eligibility criteria (Table 1). The study was promoted as an opportunity to receive at-home, self-administered HIV testing. Advertisements were geotargeted to individuals using apps inside the United States and the US territories.

Figure 1. *Together 5000* example recruitment advertisement.

Table 1. Eligibility criteria for the *Together 5000* cohort study.

Eligibility criteria	Participants (N=8777), n (%)
Core eligibility criteria (all participants must meet all of these criteria)	
Aged 16 to 49 years	8777 (100.00)
At least 2 male sex partners in the past 90 days	8777 (100.00)
Not currently participating in a clinical trial for an HIV vaccine or pre-exposure prophylaxis	8777 (100.00)
Not currently on pre-exposure prophylaxis	8777 (100.00)
Never diagnosed with HIV (self-report)	8777 (100.00)
Currently residing in the United States or territories	8777 (100.00)
Not cisgender female	8777 (100.00)
Additional eligibility criteria (participants must meet at least 1)	
>1 receptive condomless anal sex acts with a male partner in the last 3 months	6968 (79.39)
>2 insertive condomless anal sex acts with a male partner in the last 3 months	5356 (61.02)
Used methamphetamines in the last 3 months	1058 (12.05)
Rectal gonorrhea/chlamydia in the last 12 months	684 (7.79)
Syphilis diagnosis in the last 12 months	402 (4.58)
Used postexposure prophylaxis in the last 12 months	219 (2.50)
Shared injection drug needles in the last 12 months	180 (2.05)

Potential participants were directed to a secure enrollment survey in their device's Web browser and presented with a screen describing study participation and eliciting informed consent. The informed consent described the incentive schedule: US $15 for completing a secondary survey (ie, 1 after the enrollment survey) if they were eligible and another US $15 for completing self-administered at-home HIV testing (ie, oral fluid sample returned to the study laboratory for testing). Additional incentives, described in the informed consent, are available to participants who complete prospective longitudinal follow-up assessments.

Enrollment

Interested individuals were screened for eligibility via a Web-based survey collecting data on sexual behavior, substance use, demographic characteristics, history of PrEP use, and history of postexposure prophylaxis (PEP) use. The survey was programmed into Qualtrics survey software and tested by study staff. Measures had been previously used by the members of the research team or were derived from the published research. Our Web-based survey was divided into thematic blocks based on question content and used adaptive questions based on survey responses from the participants. Examples include survey questions about known HIV status, PrEP use, and main sexual partners. Survey items were not randomly ordered by participant. The number of items answered by the participants and displayed per page of the Web-based survey varied by subject and participant responses because of the skip and/or display logic used within the survey. However, to improve ease of use on mobile devices and reduce survey fatigue, each page contained 1 to 2 questions. Participants could not click back to view or change a previous response because of the skip and/or display logic depending on previous responses. If a participant chose an incorrect response, they could contact the study staff to reset that response. Before activating the survey, members of the study staff tested the survey extensively for usability and technical function. The survey was tested on Windows, Mac, iOS, and Android devices and on Chrome, Firefox, Internet Explorer, Opera, and Safari Web browsers. Eligible and consenting individuals were asked to provide contact information for longitudinal follow-up. All participants were assigned a unique identifier at study enrollment and this unique identifier was used for all study databases and datasets. Participants' contact information was stored in an encrypted database separated from their questionnaire answers and other study-related information. Only designated study staff were allowed access to study databases.

Enrolled individuals were sent a secondary Web-based survey that assessed the psychosocial characteristics. As the study participation involved receiving and returning an at-home HIV test kit via mail, as well as follow-up HIV test kits, consenting participants were required to provide name, mailing address, email address, and other contact information. We followed established and effective measures to minimize repeat participation and fraudulent manipulation of HIV testing procedures, including recording internet protocol addresses of participants and using cookies to block repeated attempts (CG et al, unpublished data, 2019). Our enrollment survey blocked multiple submissions, our databases flagged duplicate contact information, and all mailing addresses were validated with the US postal service. Multiple entries were identified by email addresses and/or phone numbers. In addition, the data manager manually checked for duplicate entries during baseline data collection. We also assessed time to completion of our Web-based surveys and checked for variability in response sets.

Upon completing this secondary survey, participants were mailed an OraSure HIV-1 specimen collection device to use at home. Participants were also provided access to a study video along with printed instructions on completing the HIV test, as well as our phone number in case they had questions. Procedures involved taking an oral swab and placing it in an oral fluid container and mailing the specimen using provided prepaid shipping materials to the Wadsworth Center Laboratory of the New York State Department of Health for antibody testing (Avioq HIV-1 Microelisa System) and archiving. Participants indicated the date of collection and any samples received by the lab after 21 days were not analyzed. In these instances, participants were contacted to retest. Median number of days between specimen collection and lab receipt was 4 days (interquartile range 3 to 6 days).

Participants With Unknown Baseline HIV Status

Participants who enrolled and completed a baseline questionnaire but did not return an HIV test kit (baseline serostatus unknown) will continue to be followed and asked at regular intervals to submit an oral fluid sample for HIV testing using the at-home sampling kit. For the purposes of prospectively estimating HIV incidence in the T5K cohort, these individuals will be excluded. However, we will conduct post hoc sensitivity analyses that make assumptions about having similar, lower, or higher HIV risk profiles than the T5K participants for whom baseline HIV status was determined.

HIV Incidence in the 12 Months Before Cohort Enrollment

We estimated pre-enrollment HIV incidence using baseline data on HIV serostatus and HIV testing history from T5K participants. Using these data, we reconstructed a cohort of individuals who could all be classified as HIV negative as of 12 months before cohort enrollment. For those HIV positive at enrollment, we estimated the time of seroconversion using self-reported data on the timing of the last HIV-negative test. Specifically, those self-reporting a negative HIV test within 6 months of T5K enrollment were classified as being HIV negative as of 6 months before enrollment, with seroconversion timing assumed to be distributed evenly during the 6 months leading up to study enrollment. Similarly, participants self-reporting a negative HIV test 7 to 12 months before T5K enrollment were classified as being HIV negative as of 12 months before enrollment, with seroconversion timing assumed to be distributed evenly during the 12 months leading up to study enrollment. We also estimated HIV incidence for the 6-month period leading up to cohort enrollment. For the purposes of identifying boundaries around minimum and maximum incidence rates, we conducted sensitivity analyses representing assumptions of the timing of seroconversion at the extremes.

Sample Size and Statistical Power

Enrollment in T5K had a targeted sample size of 5000 participants with a confirmed HIV-negative test for prospective follow-up. The 5000 number was chosen to provide precise estimates of HIV incidence of 1.11 per 100 person-years (193 seroconversions of 17,329 person-years of follow-up over 48 months). This sample size also allows 80% power to detect binary exposures with frequencies between 20% and 80% for adjusted relative hazards ranging from 1.73 to 2.27 as statistically significant.

Data Management and Analysis

All data from the Web-based surveys and the laboratory testing were imported, cleaned, and merged using SAS. Data were geocoded to an exact address or Zone Improvement Plan (ZIP) code. Maps were created in ArcGIS and did not include exact participant location.

Ethical Approval

The T5K study protocol was approved by the Institutional Review Board of the City University of New York (CUNY) Graduate School of Public Health and Health Policy.

Results

Cohort Eligibility and Recruitment

In total, 43,161 individuals began our enrollment survey and 22,091 (22,091/43,161, 51.18%) completed it (Figure 2). Of the noncompleters (N=21,070), 61.04% (12,862/21,070) closed their browser window on the informed consent page (ie, immediately). Of the completers (N=22,091), 9193 (9193/22,091, 41.61%) were eligible; however, 1023 were excluded because we determined their response to be a duplicate entry. Of the remaining 8807 participants who provided informed consent to participate in the study, 30 were excluded, as they did not provide contact information.

Enrollment

The final sample was 8777 consented participants from all 50 US states, Puerto Rico, and Guam (Figure 3). The descriptive statistics of the cohort and HIV incidence rates calculated included responses from enrolled participants meeting the eligibility criteria and completing questionnaires.

Figure 2. Consolidated Standards Of Reporting Trials diagram illustrating enrollment in the *Together 5000* cohort study. (a) 9 participants told us they tested HIV-positive outside of the study while we were in the process of trying to collect an HIV test kit from them. These participants declined to complete testing with us. (b) One participant who tested HIV-positive with our test reported an HIV-negative result from outside of the study. (c) One participant who tested HIV-negative with our test reported an HIV-positive test from outside of the study.

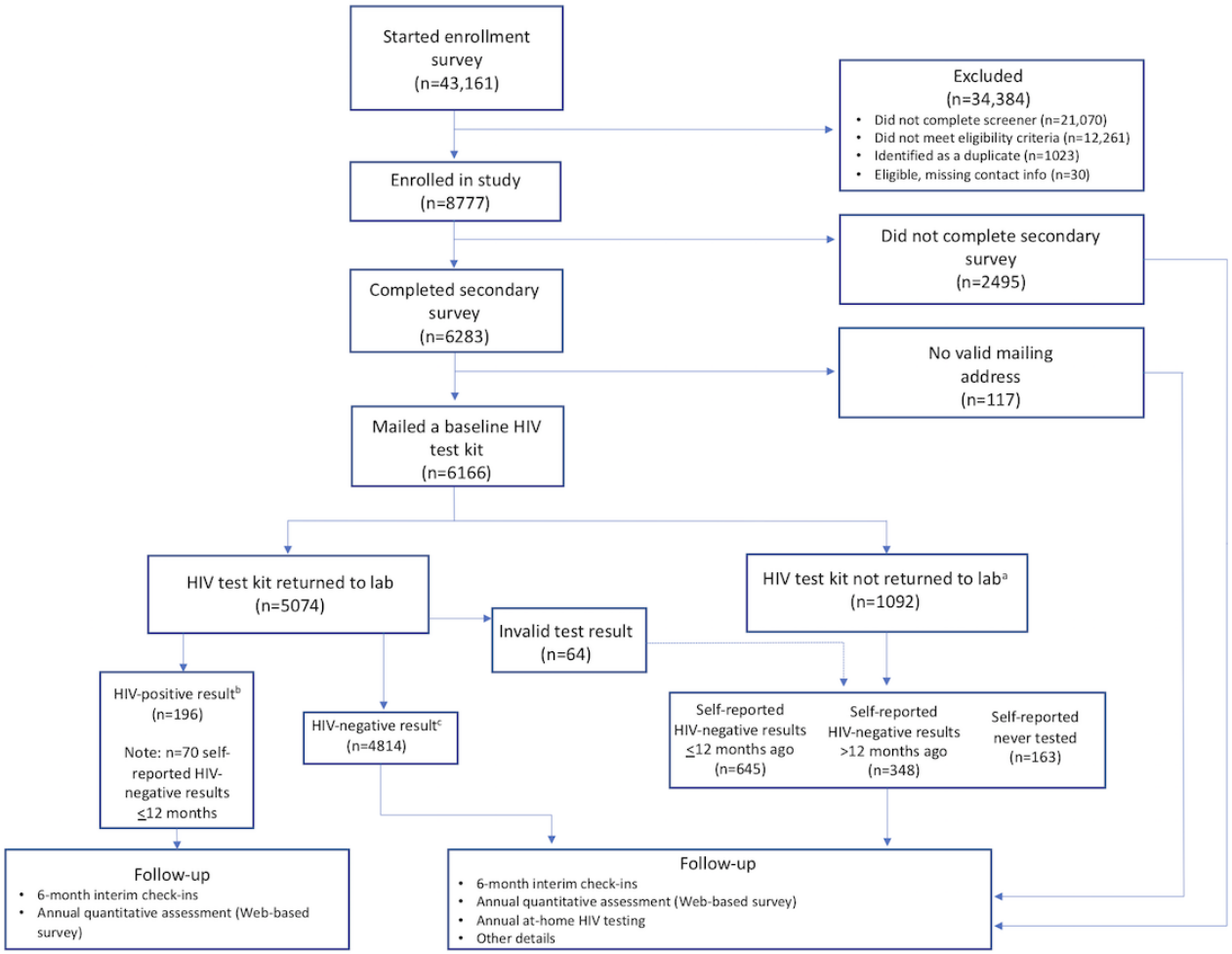
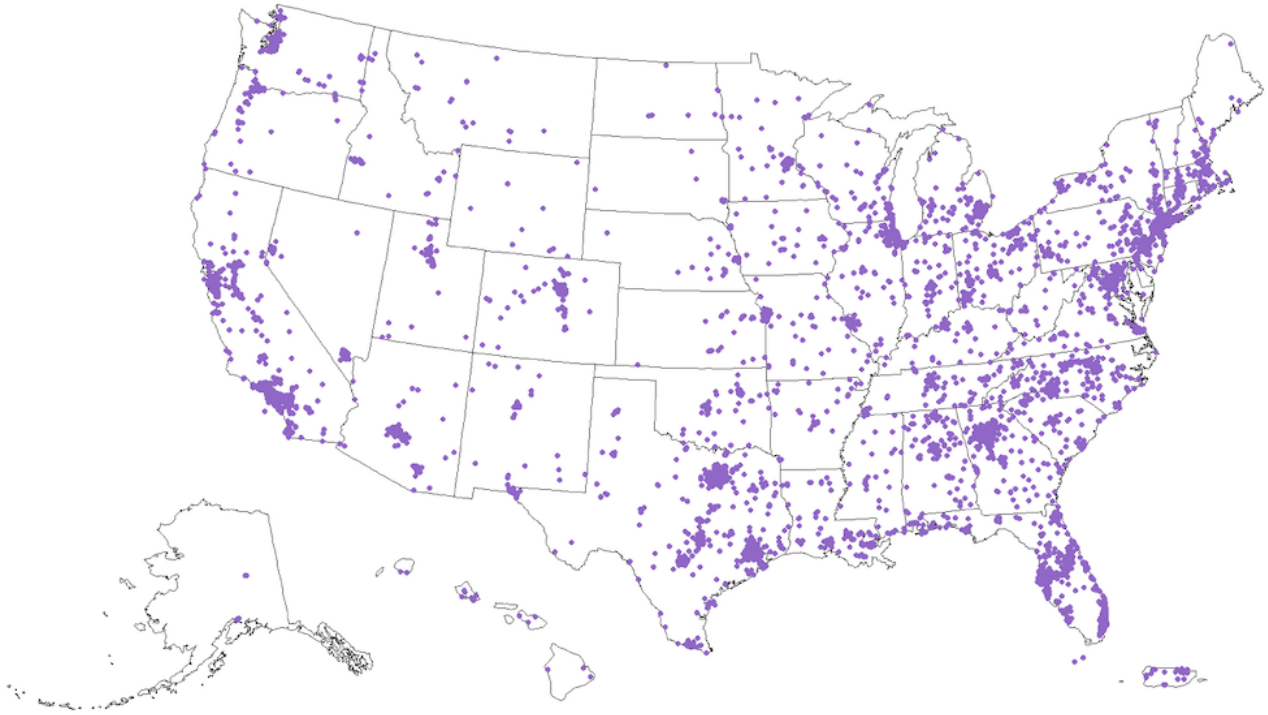


Figure 3. Geographic distribution of the *Together 5000* cohort.



Baseline Characteristics of the *Together 5000* Cohort

The final cohort of 8777 individuals was geographically diverse, including participants from all 50 US states, Puerto Rico, and Guam (Figure 3). Nearly all (8554/8777, 97.46%) were cisgender male, 0.72% (63/8777) were transgender women, and 0.60% (53/8777) were transgender men who have sex with men (Table 2). There were also 107 (107/8777, 1.22%) individuals who self-identified outside of the gender binary—all reported being assigned male sex at birth. In total, 50.91% (4468/8777) were persons of color, and 25.30% (2221/8777) were young individuals aged 16 to 24 years.

Table 2. Characteristics *Together 5000* participants at the time of enrollment.

Variable	Participants (N=8777), n (%)	Never on PrEP[a] (N=7525), n (%)	History of PrEP (N=1252), n (%)	Chi-square value (*df*)	*P* value
Race/ethnicity				10.2 (4)	.04
White	4309 (49.09)	3672 (48.80)	637 (50.88)	—[b]	—
Black	1156 (13.17)	1009 (13.41)	147 (11.74)	—	—
Latino	2227 (25.37)	1932 (25.67)	295 (23.56)	—	—
Asian/Pacific Islander	311 (3.43)	253 (3.36)	58 (4.63)	—	—
Multiracial/other	774 (8.82)	659 (8.76)	115 (9.19)	—	—
Gender				16.0 (3)	.001
Cis male	8554 (97.46)	7343 (97.58)	1211 (96.73)	—	—
Transwoman	63 (0.72)	59 (0.78)	4 (0.32)	—	—
Transman	53 (0.60)	44 (0.58)	9 (0.72)	—	—
Nonbinary (male at birth)	107 (1.22)	79 (1.05)	28 (2.24)	—	—
Sexual identity				39.6 (2)	<.001
Gay identified	7314 (83.33)	6194 (82.31)	1120 (89.46)	—	—
Bisexual identified	1346 (15.33)	1223 (16.25)	123 (9.82)	—	—
Neither/other	117 (1.33)	108 (1.44)	9 (0.72)	—	—
Age (years)				98.2 (6)	<.001
16-19	517 (5.89)	498 (6.62)	19(1.52)	—	—
20-24	1704 (19.41)	1523 (20.24)	181 (14.46)	—	—
25-29	2360 (26.89)	2003 (26.62)	357 (28.51)	—	—
30-34	1664 (18.95)	1373 (18.25)	291 (23.24)	—	—
35-39	1186 (13.51)	971 (12.90)	215 (17.17)	—	—
40-44	738 (8.41)	625 (8.31)	113 (9.03)	—	—
45 and older	608 (6.93)	532 (7.06)	76 (6.07)	—	—
No health insurance[c] (valid N=6283)	1575 (25.07)	1363 (25.32)	212 (23.56)	2.9 (1)	.23
HIV risk factors					
Recent sexually transmitted infection diagnosis (last 12 months)	1629 (18.56)	1243 (16.52)	386 (30.83)	145.5 (1)	<.001
Syphilis in lifetime	1359 (15.48)	1042 (13.85)	317 (25.32)	108.0 (1)	<.001
Syphilis in the last 12 months	402 (4.58)	303 (4.03)	99(7.91)	115.8 (1)	<.001
Rectal gonorrhea/chlamydia in the last 12 months	684 (7.79)	489 (6.50)	195 (15.58)	332.5 (1)	<.001
Oral gonorrhea/chlamydia in the last 12 months	1309 (14.91)	958 (12.73)	351 (28.04)	198.1 (1)	<.001
>1 receptive condomless anal sex acts with male in the last 3 months	6968 (79.39)	5973 (79.38)	995 (79.47)	0.01 (1)	.94
>2 insertive condomless anal sex acts with male in the last 3 months	5356 (61.02)	4545 (60.40)	811 (64.78)	8.6 (1)	.003
Having taken PEP[d] in the last 12 months	219 (2.50)	93 (1.24)	126 (10.06)	733.5 (1)	<.001
Methamphetamine use in the last 3 months	1058 (12.05)	875 (11.63)	183 (14.62)	9.0 (1)	.003
Sharing needles in the last 12 months	180 (2.05)	144 (1.91)	36 (2.88)	6.1 (1)	.05
Sex work in the last 3 months	1339 (15.26)	1127 (14.98)	212 (16.93)	3.2 (1)	.08
No primary health care provider[c] (valid N=6283)	3057 (48.66)	2700 (50.15)	357 (39.67)	34.0 (1)	<.001
Disclosed sexual behavior to health care provider[e] (valid N=3226)	2343 (72.63)	1848 (78.87)	495 (91.16)	112.1 (1)	<.001

Variable	Participants (N=8777), n (%)	Never on PrEP[a] (N=7525), n (%)	History of PrEP (N=1252), n (%)	Chi-square value (*df*)	*P* value
Never heard of PrEP	476 (5.42)	476 (6.33)	0 (0.0)	—	—
HIV testing history				414.9 (2)	<.001
<12 months ago	5362 (61.09)	4277 (56.84)	1085 (86.67)	—	—
12 or more months ago	2292 (26.11)	2145 (28.50)	147 (11.74)	—	—
Never had an HIV test	1123 (12.79)	1103 (14.66)	20 (1.60)	—	—

[a]PrEP: pre-exposure prophylaxis.

[b]Not applicable.

[c]Among those who completed our secondary survey.

[d]PEP: postexposure prophylaxis.

[e]Among those who completed our secondary survey and reported having a health care provider.

HIV Risk

Per eligibility criteria, at enrollment, all T5K participants reported sex with >2 male partners in the 90 days before enrollment, were HIV negative, and were not taking PrEP. In addition, 79.40% (6969/8777) reported >2 insertive condomless anal sex (CAS) acts, 61.02% (5356/8777) reported >1 receptive CAS acts in the past 90 days (Table 2), 2.50% (219/8777) reported having taken HIV PEP in the last 12 months, 18.56% (1629/8777) reported having a sexually transmitted infection (STI) diagnosis in the last 12 months, including rectal (684/8777, 7.79%) or oral (1309/8777, 14.91%) gonorrhea/chlamydia, and 15.48% (1359/8777) reported a lifetime syphilis diagnosis. However, only 14.26% (1252/8777) reported ever having taken PrEP. Nearly half (3057/6283, 48.66%) reported not having a primary health care provider, and 12.79% (1123/8777) said that they had never tested for HIV.

History of Pre-Exposure Prophylaxis Use

In Table 2, we compare participants who reported never having taken PrEP (7525/8777, 85.74% of enrolled) with those who reported having taken PrEP previously (1252/8777, 14.26% of enrolled). Previous PrEP users were significantly more likely to be white, gay-identified, and older and have tested for HIV in the last 12 months—as well as reported significantly more HIV risk factors (past year STI diagnosis, past year PEP use, and >2 insertive CAS acts with male partners in the last 3 months). Participants with a history of PrEP use were significantly more likely to have used PEP (10.1% vs 1.2%; *P*<.001) and have had a primary health care provider (and be open about their sexual behavior with men to that provider).

Completion of Baseline HIV Test

Of the 8777 participants enrolled, 6166 (70.25%) provided valid mailing addresses on the second survey and were sent an at-home HIV testing kit, and 5074 participants provided a sample to test (5074/6166, 82.29% of those sent a kit and 5074/8777, 57.81% of those enrolled). Compared with participants who did not provide a sample for testing (3703), those who did provide a sample (5074) were significantly more likely to report income >US $50,000 (22.12% vs 26.25%; *P*<.001), be white (43.64% vs 53.07 *P*<.001), have a college degree (29.78% vs 40.69%; *P*<.001), and be slightly older on average (29.81 vs 30.84 years; *P*<.001).

HIV Status and Estimating the Cohort HIV Incidence Rate Before Together 5000 Study Enrollment

Table 3 describes the outcomes of baseline HIV testing. Of 5074 persons who returned their test kit, 196 (196/5074, 3.86%) had undiagnosed HIV. Of those 196, individuals self-reported that (1) they had a negative HIV test within 6 months of T5K enrollment (n=34), (2) they had a negative HIV test within 7 to 12 months of T5K enrollment (n=36), (3) they had a negative HIV test more than 12 months before T5K enrollment (n=95), or (4) they had never tested for HIV before T5K enrollment (n=31). As an upper bound, we calculated the incidence rate for the extreme scenario that assumes all 196 persons seroconverted during the 12 months before study enrollment (Table 4). Using these approaches, we estimated that the incidence rate in this cohort in the 12-month period leading up to T5K study enrollment was 2.42 (95% CI 2.02-2.90) per 100 person-years. The estimate for the 6-month period leading up to enrollment was 2.16 (95% CI 1.63-2.81). Alternate scenarios under different assumptions about the timing of seroconversion for persons with either less recent HIV tests or no history of HIV testing gave slightly higher incidence estimates, ranging from 2.74 to 3.76 per 100 person-years. The maximum HIV incidence estimate was 3.98 (95% CI 3.45-4.57) per 100 person-years, which assumed that all 196 persons testing HIV positive had seroconverted in the 12 months before study enrollment (Multimedia Appendix 1). Although no participants were on PrEP at enrollment, when comparing the crude prestudy incidence rates for those never on PrEP to those with a history of PrEP, the incidence rate was higher for both the 6-month (incidence rate ratio [IRR]: 1.62; 95% CI 0.69-4.61) and the 12-month (IRR: 2.35; 95% CI 1.21, 5.20) periods before enrollment.

Table 3. HIV testing outcomes among *Together 5000* study population.

Variable	Total participants (N=8777), n (%)	Never on PrEP[a] (N=7525), n (%)	History of PrEP N=1252), n (%)	Chi-square value *(df)*	*P* value
Returned HIV test kit to the lab	5074 (57.81)	4343 (57.71)	731 (58.39)	0.2 (1)	.66
HIV test-kit results[b]	—[e]	—	—	14.6 (1)	<.001
HIV-negative test result	4814 (94.88)	4101 (94.43)	713 (97.54)	—	—
HIV-positive test result	196 (3.86)	186 (4.28)	10 (1.37)	—	—
Date of most recent HIV test[d]	—	—	—	5.0 (3)	.18[e]
Self-reported HIV-negative test <6 months ago	34 (17.35)	30 (16.12)	4 (40.00)	—	—
Self-reported HIV-negative test 7-12 months ago	36 (18.37)	34 (18.28)	2 (20.00)	—	—
Self-reported HIV-negative test >12 months ago	95 (48.47)	91 (48.92)	4 (40.00)	—	—
No previous HIV test	31 (15.82)	31 (16.67)	0 (0.00)	—	—

[a]PrEP: pre-exposure prophylaxis.

[b]N=n value from returned HIV test.

[c]Not Applicable.

[d]N=n value from HIV-positive test result.

[e]Mid *P* exact test.

Table 4. HIV incidence estimates among *Together 5000* study population in the 12- and 6-month periods before study enrollment.

Period before enrollment	All participants	No history of PrEP[a] use	History of PrEP use	Incidence rate ratio
12-month period before enrollment				
Number of presumed recent seroconversions, n (%)	118 (100)	110 (93)	8 (7)	—[b]
Person-years at risk among seroconverters	58.75	54.75	4	—
Person-years at risk among HIV-negative persons	4814	4101	713	—
Incidence rate per 100 person years (95% CI)	2.41 (2.02-2.90)	2.63 (2.19-3.19)	1.12 (0.52-2.13)	2.36 (1.21-5.20)
6-month period before enrollment				
Number of presumed recent seroconversions, n (%)	52 (100)	47 (90)	5 (10)	—
Person-years at risk among seroconverters	13.0	11.8	1.3	—
Person-years at risk among HIV-negative persons	2407	2051	357	—
Incidence rate per 100 person-years (95% CI)	2.15 (1.63-2.81)	2.28 (1.70-3.01)	1.40 (0.52-3.12)	1.63 (0.69-4.61)

[a]PrEP: pre-exposure prophylaxis.

[b]Not applicable.

Longitudinal Follow-Up and Measurements

Prospective closed follow-up of T5K participants includes completion of an annual self-administered at-home HIV testing and extensive Web-based surveys beginning 12 months after the baseline survey. In addition, participants will be contacted every 6 months (in between annual surveys) for a brief survey on HIV testing, diagnosis, and PrEP use (ie, attempts to access PrEP, PrEP initiation, PrEP adherence, and PrEP discontinuation). Participants who self-report being on PrEP are asked to provide proof in the form of a picture of the medication bottle with their prescription information. A comprehensive list of key study measurements by study wave is included in Table 5. We will follow the cohort of 8777 individuals for up to 4 years to characterize the following: the rate of PrEP uptake/discontinuation; individual /network /contextual-level determinants of PrEP uptake /discontinuation; patterns of PrEP use (eg, daily or on demand); the rate of new HIV seroconversions and other missed HIV prevention opportunities (ie, STIs while not on PrEP); individual/network/contextual-level determinants of HIV seroconversion and missed HIV prevention opportunities; racial/ethnic disparities in HIV incidence and their trends over time; and the influence of PrEP uptake on racial/ethnic disparities in HIV incidence.

Table 5. Follow-up measures in the *Together 5000* cohort.

Measures[a]	Number of items	Administered at					
		Enrollment survey	Secondary survey	12 months	24 months	36 months	48 months
Sociodemographic questionnaire	14	X[b]	—[c]	X	X	X	X
PrEP[d] and PEP[e] history	5	X	—	X	X	X	X
Men who have sex with men risk index[f]	10	X	—	X	X	X	X
History of sexually transmitted infections and HIV testing	13	X	—	X	X	X	X
Main sexual partner	7	X	—	X	X	X	X
Drug, alcohol, and cigarette use	4	X	—	X	X	X	X
Incarceration and recent arrest	3	—	X	X	X	X	X
Connor-Davidson resilience scale	10	—	X	X	X	X	X
Alcohol, smoking, and substance involvement screening test	13-86	—	X	X	X	X	X
Alcohol use disorder identification test	10	—	X	X	X	X	X
Generalized anxiety disorder	2	—	X	X	X	X	X
Patient health questionnaire	2	—	X	X	X	X	X
Internalized homophobia scale	14	—	X	X	X	X	X
Lesbian, gay, bisexual, and transgender resources and policies	14	—	X	X	X	X	X
General PrEP experiences and acceptability	12	—	X	X	X	X	X
Barrier to PrEP uptake	14	—	X	X	X	X	X
Partner violence questionnaire	12	—	X	X	X	X	X
Hepatitis C virus risk score	6	—	X	X	X	X	X
Multidimensional scale of perceived social support	12	—	X	X	X	X	X
Multidimensional peer-victimization scale[g]	14	—	X	—	—	—	—
Position preference	1	—	X	—	—	—	—
Sexual debut and childhood sexual abuse	7	—	X	—	—	—	—

[a]There are brief check-in surveys at 6, 18, 30, and 42 months.

[b]Construct is assessed.

[c]Construct is not assessed.

[d]PrEP: pre-exposure prophylaxis.

[e]PEP: postexposure prophylaxis.

[f]Modified to include questions about female, transmale, and transfemale sex partners and condomless sex acts with female sex partners.

[g]Provided as published scale to currently enrolled high school students, modified from *past year* to *when you were in high school* for older participants, added 2 questions regarding missing school in the last year and whether the scale items occurred on the Web.

Given the novel nature of this entirely Web-based nationwide cohort, we elected to longitudinally follow *all* participants providing consent at enrollment (N=8777), rather than only those who completed HIV testing. Participants who did not complete the secondary survey or subsequent HIV testing will have the opportunity to provide those data/samples at future assessments, and this will enable us to learn more about differential rates of participation and attrition in the cohort moving forward.

Observed Seroconverters

Participants who were HIV negative at baseline and who indicate that they tested HIV positive between study assessments will be asked and incentivized to provide HIV status documentation and will not be asked to complete additional HIV tests for study purposes. These participants will be classified as recent seroconverters. Among the remaining participants, those who test positive in the 12-month home test will also be classified as recent seroconverters, and those who test negative will be classified as remaining seronegative. We will contact recent seroconverters to capture information about and facilitate the process of linkage to care. In addition to referral for treatment, approximately 3 months after their diagnosis via the study, we will invite a sample of seroconverting participants to complete a semistructured individual telephone interview to identify missed HIV prevention opportunities and barriers/facilitators

of their entry into HIV care and subsequent retention. We will follow these participants until the end of the study to document movement through the HIV care continuum [14,15].

Discussion

Principal Objectives

We have successfully recruited an entirely Web-based national cohort of confirmed HIV-negative men, transgender men, and transgender women who have sex with men and are at very high risk for HIV into longitudinal follow-up. Importantly, none of the T5K cohort members were on PrEP at enrollment but all met the objective criteria for PrEP use. This will allow our study to fill critical knowledge gaps that can improve the understanding of barriers to PrEP uptake and engagement among those most in need of HIV prevention interventions. This cohort also offers opportunities to examine the effect of different implementation strategies aimed at improving the uptake of and engagement with HIV prevention interventions, including those that can be delivered on the Web.

We observed a higher rate of several recent and lifetime STIs among persons with a history of PrEP compared with those who were never on PrEP. This could represent differences in the risk profile of persons who have used PrEP (ie, they were at higher risk for an STI in the past before or while using PrEP). However, many STIs are asymptomatic, making it likely that the STIs reported by this group at baseline would have been diagnosed as a result of them having initiated PrEP in the past, as PrEP services involve baseline and follow-up STI screening and treatment. We also observed that those with a history of PrEP were >8 times more likely to have taken PEP in the past. This could reflect better access to HIV prevention services or greater HIV risk among those with a history of PrEP use. Persons on PEP are usually good candidates for PrEP, and PrEP should be systematically discussed and offered to all persons completing PEP if there is a likelihood of ongoing HIV risk.

Our estimates of HIV incidence in the 12-month period leading up to T5K cohort enrollment (2.4% per year overall and 2.6% per year among those never on PrEP) suggest that the risk of HIV acquisition that we will observe prospectively will also be quite high, unless PrEP uptake increases dramatically. Indeed, we observed that HIV incidence was substantially higher among those never on PrEP compared with those with a history of PrEP before enrollment (IRR 2.36; 95% CI 1.21-5.20).

Strengths

Major strengths of this cohort study include the large sample size, the wealth of self-reported information related to HIV risk and PrEP, direct measurement of HIV status and seroconversion, geographic representativeness, recruitment of participants independent of their access to/engagement with the health care system, and inclusion of large numbers of racial/ethnic minority GBM as well as those aged <25 years. Having every US state, Puerto Rico, and Guam represented allows for a robust exploration of state-level policies and other higher-level effects (ie, contextual factors) as potential determinants of PrEP uptake and HIV risk. More than 50% (4468/8777, 50.91%) of the cohort comprises HIV-negative men of color, allowing in-depth investigations into the mechanisms of racial/ethnic disparities in PrEP uptake, HIV incidence, and circumstances surrounding HIV seroconversion. Importantly, the T5K cohort study design, with semiannual Web-based at-home surveys and at-home self-sampling for HIV testing, reduces the potential for participation and questionnaire-response bias introduced by the Hawthorne effect, which could be stronger in face-to-face studies. Studies involving frequent face-to-face contact can cause participants to adopt behaviors that make them less representative of the high-risk populations from which they were drawn. Of note, McCabridge et al [16] introduced the construct of *research participant effects* that was built upon the Hawthorne effect [17] by elaborating on the implications of research on the mechanisms that introduce bias, including demand characteristics [18,19]. Studies involving high levels of staff contact with participants may induce behavior change by repeatedly engaging participants outside of their natural context, artificially influencing results [17,19,20] and reducing generalizability [21].

Weaknesses

Recruiting participants and gathering data on the Web is a much less controlled research environment than face-to-face or telephone interview studies. Web-based recruitment also increases our vulnerability to repeat participation and fraudulent manipulation of HIV testing procedures (eg, someone else's saliva, other than that of the enrolled participant, could be submitted to the lab). However, we followed established and effective measures to minimize these risks [22,23]. Although we took steps to assess whether participants were reading the interview questions, participants recruited on the Web may be less cognitively engaged in questionnaire completion and less inclined to provide a specimen than if they were interacting directly with study personnel. Our study population was recruited via sexual networking apps and represented a sample of those at high risk for HIV, who are not on PrEP at cohort enrollment. However, the underlying population that gave rise to the T5K cohort is not representative of all HIV-negative GBM at high risk for HIV in the United States [24]. Finally, HIV seroconversions and PrEP uptake may be incompletely ascertained, and the timing of HIV seroconversions must be estimated using a midpoint approach with broad intervals, potentially introducing bias in our baseline HIV incidence estimates. For example, our study eligibility/inclusion criterion of *never diagnosed with HIV (self-report)* effectively excludes frequent HIV testers who seroconverted and were diagnosed in the period immediately before study launch.

Challenges and Lessons Learned

There have been many challenges and lessons learned in the launch and execution of the T5K study, which have been detailed elsewhere ([13]; also CG et al, unpublished data, 2019). In brief, although there are many advantages to entirely Web-based studies, challenges we have encountered include greater difficulty obtaining signed informed consent, returning HIV test results to participants, linking persons to HIV services when needed (especially in underserved areas), the potential for participants to be distracted, and difficulty ensuring unique

and valid participants—and new challenges with regard to privacy and data security.

Applications for Clinical and Population Health Intervention Studies

Intervention studies are of great interest to the T5K study team. Our goal is to utilize key findings from this cohort to develop interventions, potentially including some delivered completely on the Web, once the observational phase is completed. There will likely be opportunity for natural experiment design studies that allow for rigorous examination of future state or national policy changes, an introduction of long-acting PrEP formulations or dosing recommendations, and other novel HIV prevention modalities. To facilitate such research, we will gather extant data via geolinking with T5K participant information [25]. These include the participant's ZIP code matched to county- and state-level data regarding, for example, STI rates, HIV incidence and prevalence, HIV viral suppression rates, residing in an Affordable Care Act Medicaid expansion state (yes/no), urban versus nonurban city/county location, state-wide PrEP policies, and pro-/anti-lesbian, gay, bisexual, and transgender policies, Human Rights Campaign state equality index [26], and the Movement Advancement Project (MAP) index [27].

Collaboration With the *Together 5000* Study Team

T5K welcomes new collaborations. Instructions and a concept proposal form are available on our website or can be obtained by emailing the Principal Investigator (CG). Submitted concept proposals will be reviewed by CG and a core group of T5K investigators, with rapid turnaround.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist for Reporting Results of Internet E-Surveys (CHERRIES) and Sensitivity analyses for HIV incidence estimates among *Together 5000* (T5K) study population.
[PDF File (Adobe PDF File), 138 KB - resprot_v8i8e13715_app1.pdf]

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Abbreviations

CAS: condomless anal sex
CUNY: City University of New York
GBM: gay, bisexual, and other men who have sex with men

IRR: incidence rate ratio
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
T5K: *Together 5000*
ZIP: Zone Improvement Plan

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Protocol

Development of Ovarian Tissue Autograft to Restore Ovarian Function: Protocol for a French Multicenter Cohort Study

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Abstract

Background: Sterility is a major late effect of radiotherapy and chemotherapy treatments. Iatrogenic sterility is often permanent and greatly impacts long-term quality of life. Ovarian tissue cryopreservation (OTC) performed before gonadotoxic treatments with subsequent autograft is a method of fertility preservation available for girls and women. Its application in prepubertal girls is of particular value as it is the only possible approach in this patient group. In addition, it does not require a delay in cancer therapy and no ovarian stimulation is needed.

Objective: The primary aim of this protocol is to help increase the implementation of ovarian tissue autografting in France. Knowledge is still lacking regarding the efficacy of ovarian transplantation in restoring ovarian function and regarding the safety of this procedure, especially the risk of cancer cell reseeding in certain types of cancer. A secondary aim of this study is to generate data to improve our understanding of these two essential aspects.

Methods: The DATOR (Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function) study is ongoing in 17 university hospitals. The DATOR protocol includes the autograft of ovarian cortex fragments. Candidates are identified from an observational prospective cohort (called the Prospective Cohort of Patients Candidates for Ovarian Tissue Autograft [PERIDATOR]) of patients who have undergone OTC. Enrollment in the study is initiated at the patient's request and must be validated by the center's multidisciplinary team and by the study steering committee. The DATOR study begins with a total medical checkup. Ovarian tissue qualification and residual disease detection, if required, are performed.

Results: The study is ongoing. Currently, 38 patients have provided informed consent and have been entered into the DATOR study. Graft has been performed for 34 of these patients. An interim analysis was conducted on the first 25 patients for whom the period of at least 1 year posttransplantation was achieved. Out of these 25 patients, 11 women succeeded in becoming pregnant (pregnancy rate=44% [11/25]; delivery rate=40% [10/25]). Among these, 6 women conceived twice, and 1 pregnancy led to a miscarriage.

Conclusions: Our preliminary analysis appears to be coherent with the accumulating body of evidence indicating the potential utility of ovarian tissue autograft for patients with premature ovarian failure. All these elements justify the pursuit of our study.

Trial Registration: ClinicalTrials.gov NCT02846064; https://clinicaltrials.gov/ct2/show/NCT02846064

International Registered Report Identifier (IRRID): DERR1-10.2196/12944

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KEYWORDS

cohort study; ovarian tissue; cryopreservation; fertility preservation; pregnancy rate; live birth rate

Introduction

Cancer is a major public health issue. Its incidence is increasing worldwide, particularly in adolescents and young adults [1-3]. Chemotherapy and/or radiotherapy have significantly improved the chances of long-term survival [4-9]. For women of reproductive age, cancer treatments, particularly those using alkylating agents, and radiation therapy directed at the pelvis or the abdomen can incur the major side effect of inducing premature ovarian failure and infertility [10-16]. The incidence of iatrogenic sterility is consequently increasing [17]. The risk is linked to the patient's age, as well as the type, amount and timing of the treatment delivered [13,18,19].

Mechanisms by which chemotherapies induce damages to ovarian reserve are partially elucidated. Treatments could deplete the primordial follicle pool by direct toxicity to follicles and/or by increasing primordial follicle activation into growing follicles [20]. In cases of pelvic irradiation, preventive surgical measure such as oophoropexy may be indicated. Nonsurgical measures (implying gonadotropin-releasing hormone or luteinizing hormone (LH)–releasing hormone inhibition) designed to minimize gonadotoxic effects might represent alternative strategies, whose efficiency is still controversial [21-28]. Recent studies indicate that primordial follicle activation modulators may provide another promising option for fertility preservation in cancer patients for whom oocyte and embryo cryopreservation are not possible. Nevertheless, they are still under trial [29-31]. A decrease in or loss of fertility is a traumatic issue that greatly impacts long-term quality of life. Several studies have reported the emotional distress of cancer survivors that became sterile [32-34]. Although a spontaneous return of ovarian function and fertility is possible, it occurs in only very few patients [35,36]. In this context, most health care providers recognize the importance of fertility preservation measures before the initiation of anticancer drugs. Nevertheless, a very small proportion of patients actually benefit from available fertility preservation procedures [37-44].

Several options can be proposed according to the patients' age, marital status, and pathology. One such fertility preservation technique is ovarian tissue cryopreservation (OTC) [45,46]. OTC is independent of ovarian stimulation and can therefore be implemented without delay. In addition, it is the only technique that can be offered to children because neither a partner nor ovarian stimulation with a pickup are required, and it is also suitable for women with hormone-sensitive cancer [12,47,48]. Laparoscopic harvesting consists of a total (unilateral) or partial oophorectomy or ovarian tissue biopsies. Ovarian cortex is frozen in fragments (1 cm/0.5 cm) according to a protocol using slow cooling with manual or automatic seeding [49,50] and then stored in nitrogen gas or liquid. Rapid freezing (vitrification) of ovarian tissue is also possible and might even be more effective than slow freezing [51-53]. Fertile oocytes can be obtained from fragments of cryopreserved ovarian cortex only by maturation of the oocytes present in the primordial, primary, and preantral follicles that have withstood the freezing-thawing process. Various research teams are working on developing in vitro folliculogenesis techniques [54-62] but also autologous transplantation of isolated follicles and subsequent ovarian reconstruction [63-67].

Ovarian tissue autograft is currently the only technique allowing natural restoration of fertility and ovarian endocrine function [68]. Once full cancer recovery is achieved, thawed tissues can be transplanted back into the patient who wishes to have a baby [69]. Ovarian tissue can be transplanted orthotopically (ie, into the pelvic cavity in or near the remaining ovary) or heterotopically (ie, extrapelvically into the forearm or the abdomen for example), the former technique being associated with greater success rates [70-73].

The first ovarian transplantations were reported by Oktay and Karlikaya in 2000 and Radford et al in 2001 [74,75]. These researchers showed a resumption of follicular development, with or without ovarian stimulation. The first human embryo was obtained in vitro in 2004 after heterotopic grafting of subcutaneous ovarian tissue, but its development stopped after its transfer into the uterine cavity [76]. The first live birth after orthotopic autotransplantation of cryopreserved ovarian tissue was described in 2004 by Donnez et al [77]. Ovarian tissue transplantation has since resulted in the birth of more than 130 babies [78,79]. Delivery rates are usually used as an indicator for success, even if not perfectly accurate (there may be more than one transplantation per woman and not every grafted woman had fertility achievement in mind). Delivery rates reported are from 15% to 50% [68,79-88].

Predictive factors that would allow the identification of the patients most likely to conceive and safely deliver healthy babies after autotransplantation have not yet been identified. Therefore, there is a need for cohort studies following patients from OTC through to the babies' first months.

In 2009, our team, in collaboration with the university hospital of Limoges (France), reported the first live birth in our country, the seventh in the world. It was the first live birth associated with a noncancerous disorder, namely sickle cell anemia treated by allogeneic bone marrow transplantation [89].

Initially, in France, ovarian tissue preservation was only authorized in the context of research protocols. Then, new legislation on Bioethics (2004) allowed for the practice of germinal tissue preservation in centers accredited by the BioMedicine Agency (Agence de BioMedecine, ABM; decree of December 22, 2006). Worldwide, thousands of patients have benefited from OTC. In France, the ABM reported that 2845 patients had their ovarian tissue cryopreserved by the end of 2016. In France, the 2008 decree relative to the rules for good clinical and biological practices for medically assisted procreation stipulates that the use of germinal tissue must remain in the field of research. A further decree published in 2017 requires that specific information on the knowledge and results generated by any research protocols must be delivered [90].

Only 3 research protocols are currently recruiting patients in our country with the aim of proposing transplantation of cryopreserved ovarian cortex in women with premature ovarian failure. One of those protocols, named CAROLéLISA (*Autograft of Human Ovarian Tissue: Efficiency and Safety*), is led by Professor Catherine Poirot in the unit of reproduction biology of Assistance Publique–Hôpitaux de Paris in Paris. The first patient was included in June 2010 and the cohort currently comprises 40 subjects. Professor Bruno Salle and Dr Jacqueline Lornage are leading a protocol in the university hospital Lyon-Bron, Lyon, but no details of the study procedures are available.

The DATOR study (Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function) (NCT02846064) was launched in 2013 with the aims of assessing the safety and efficacy of ovarian tissue autotransplantation in terms of restoration of ovarian function and fertility. This evaluation will take into account graft survival in the short-to-medium term.

Methods

Design and Objectives

The DATOR study is a multicenter prospective longitudinal cohort project. Candidates for the DATOR study are identified from an observational prospective cohort (named Prospective Cohort of Patients Candidates for Ovarian Tissue Autograft [PERIDATOR]) of patients who have undergone OTC. The PERIDATOR cohort specifically aims to record the number and describe the profile of patients who have undergone OTC in the participating hospitals. The DATOR study allows the dissemination of the orthotopic 2-step surgical technique in France, thus making it available to a greater number of patients.

Participants

The DATOR protocol was initially conducted in 12 French university hospitals, and a total of 17 centers are now recruiting (Besançon, Limoges, Toulouse, Rouen, Bordeaux, Clermont-Ferrand, Strasbourg, Clamart, Nantes, Marseille, Lille, Reims, Bondy, Grenoble, Nancy, Tenon, and Poissy). In each center, each case is discussed within a multidisciplinary team including biologists, surgeons, gynecologists, hematologists, oncologists, pathologists, endocrinologists, and/or pediatricians.

Study Size

After a preliminary survey of the 12 centers that were among the first to participate, the number of patients eligible was estimated at 186, out of a total of 650 cryopreservations performed in those centers at that time. Recruitment began in 2013.

Regarding the DATOR study, an authorization was originally obtained for 10 transplantations over a 2-year period. A first protocol modification extended the number of grafts allowed to 20. Two 24-month extensions of the inclusion period were granted in 2017 and in 2018. Therefore, the inclusion period now extends from 2013 to 2021 with a 3-year follow-up to achieve 62 ovarian transplantations.

Recruitment

The inclusion criteria for both the PERIDATOR cohort and the DATOR study are as follows: women between 18 and 43 years of age, who underwent ovarian tissue cryopreservation, and cured of their primary disease.

Specific inclusion criteria for the PERIDATOR cohort are as follows: short- or medium-term childbearing desire and premature ovarian failure documented by ultrasound criteria (antral follicle counts <5) and hormonal criteria (anti-Müllerian hormone [AMH] <2 ng/mL, even if follicle-stimulating hormone [FSH] <20 IU/L).

Specific inclusion criteria for the DATOR study are as follows: short-term childbearing desire; total premature ovarian failure defined, in the absence of hormone therapy, by the association of suggestive clinical criteria (secondary amenorrhea, flushes, signs of estrogen deficiency, etc), ultrasound criteria (absence of antral follicle), and hormonal criteria: FSH >20 IU/L, AMH <2 ng/mL, and low estradiol level; and patients included retrospectively, that is, patients who have already undergone ovarian tissue autograft.

Exclusion criterion is patients under legal protection.

Inclusion in the Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function Study

Patient included in the PERIDATOR cohort are followed up annually after OTC and after the end of the gonadotoxic therapy (clinical, hormonal, and ultrasound workup with the biologists and gynecologists in the treating center). Adult patients who wish to conceive a child can make a request to undergo ovarian tissue autograft. Participation in the DATOR study is then proposed, and if the patient accepts, then the case is discussed in the multidisciplinary meeting in the treating center.

Pretransplantation Workup and Biological Qualification of the Grafts

The clinical examination includes the search for clinical signs of primary ovarian insufficiency (absence of menstrual cycles and hot flushes). The administration (or not) of hormone replacement therapy is recorded. The mandatory blood tests required for medically assisted procreation as well as hormone tests (FSH, LH, AMH, inhibin B, and estradiol) are performed. Pelvic ultrasound with Doppler is performed to assess the size of the uterus and the remaining ovary (-ies) and the thickness of the endometrium under hormone replacement therapy. Finally, a preoperative consultation with an anesthesiologist is also performed.

To complete the pretransplant workup, biological qualification of the grafts is performed. One of the fragments of cryopreserved ovarian tissue, selected at random, is thawed according to the protocol validated for the actual transplant. The majority of the thawed fragment is then prepared for pathological examination, and the remainder is used to evaluate the long-term viability of the isolated ovarian follicles. The pathology exam evaluates the quality of the tissue after the freeze-thaw cycle and the abundance of follicles, and it also investigates the presence of any potential anomalies, in particular the presence of residual malignant cells in cases where the initial pathology was cancer.

If the number and quality of follicles are found to be low, then the number of fragments of ovarian cortex to be used for the autograft can be increased. Microbiological controls are performed on the freezing, thawing, and transport media of the fragment under investigation.

The possible reseeding of malignant cells during the autograft of ovarian fragments is a problem of great importance. Acute leukemia is the most common childhood cancer. Performing autotransplantation on patients at high risk of cancer reseeding (ie, acute leukemia) is not recommended because of the high risk of cancer cell reintroduction [91,92]. The clinical decision requires the use of minimal residual disease detection techniques, molecular analysis [93-95], flow cytometry [96,97], and xenograft [98,99].

Decision of the Steering Committee

The local investigating centers put together a file that is subsequently submitted to the steering committee of the DATOR study. The steering committee is composed of experts from the multidisciplinary teams of various university hospitals in France. The steering committee evaluates the rational for the autograft, and the risk-benefit ratio (quality of the preserved fragments, obstetrical risk, and cancer risk). The steering committee may call on outside experts, if necessary. The decision of the steering committee takes account of the progress in techniques that make it possible to assess residual disease in the ovaries. After evaluation of the file, the steering committee approves (or does not approve) the ovarian transplantation.

Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function Protocol

Graft Thawing and Preparation

The freezing and thawing protocol for ovarian tissue has previously been described and established in the laboratory [89]. The thawing of the ovarian fragments is carried out sterilely in class A, under a hood, in the laboratory of the assisted reproductive technology (ART) center. After quickly thawing the vials, the strips are washed in decreasing solutions of DMSO 1.5 M (5 min), 1 M (5 min), 0.5 M (10 min), and 0.05 mol/L sucrose in Leibovitz L-15 medium supplemented with 10% decomplemented patient serum. The strips are then rinsed and transferred to the operating theater for the graft in medium containing 20% serum only.

Regarding the second step of the transplantation, if the size of the fragments of ovarian cortex is less than 0.5 cm^2, several fragments can be sutured in an *ovarian patch* of 2 cm^2 by the surgeon in the laboratory under a laminar flow hood.

Autograft

Surgeons from each of the centers participating in the study have been trained in the autograft technique for the implantation of cryopreserved ovarian tissue by Dr Pascal Piver who proctored the first autografts in all centers.

The 2-stage orthotopic graft is the first-line technique used in this study [89]. The transplantation is performed in 2 stages by celioscopy under general anesthesia. It can also be performed with the aid of a surgical robot in centers equipped with such facilities and who are trained in its use. Heterotopic transplantation can be proposed if a contraindication exists to orthotopic transplantation.

Follow-Up in the Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function Study

To collect outcome data to evaluate the success of the autograft, monthly follow-up is performed for 1 year after the transplant or until the patient becomes pregnant. The monthly follow-up includes clinical, biological, and ultrasound examination. The clinical evaluation is performed by the gynecologists and biologists of the ART unit in the participating center. They investigate for clinical signs of recovery of ovarian function (onset of spontaneous menstrual cycles or disappearance of hot flushes). Biological follow-up includes hormone tests (FSH, LH, AMH, inhibin B, estradiol, and progesterone). Normalization of endogenous gonadotropins is also investigated. While awaiting this stage, hormone replacement therapy and administration of vitamin are pursued.

Echographic follow-up comprises transvaginal ultrasound of the grafts (presence of antral follicles) associated with Doppler examination to evaluate neovascularization. Magnetic resonance imaging is performed 3 months after the transplantation to assess the state of revascularization of the grafts and to determine the origin of neovascularization.

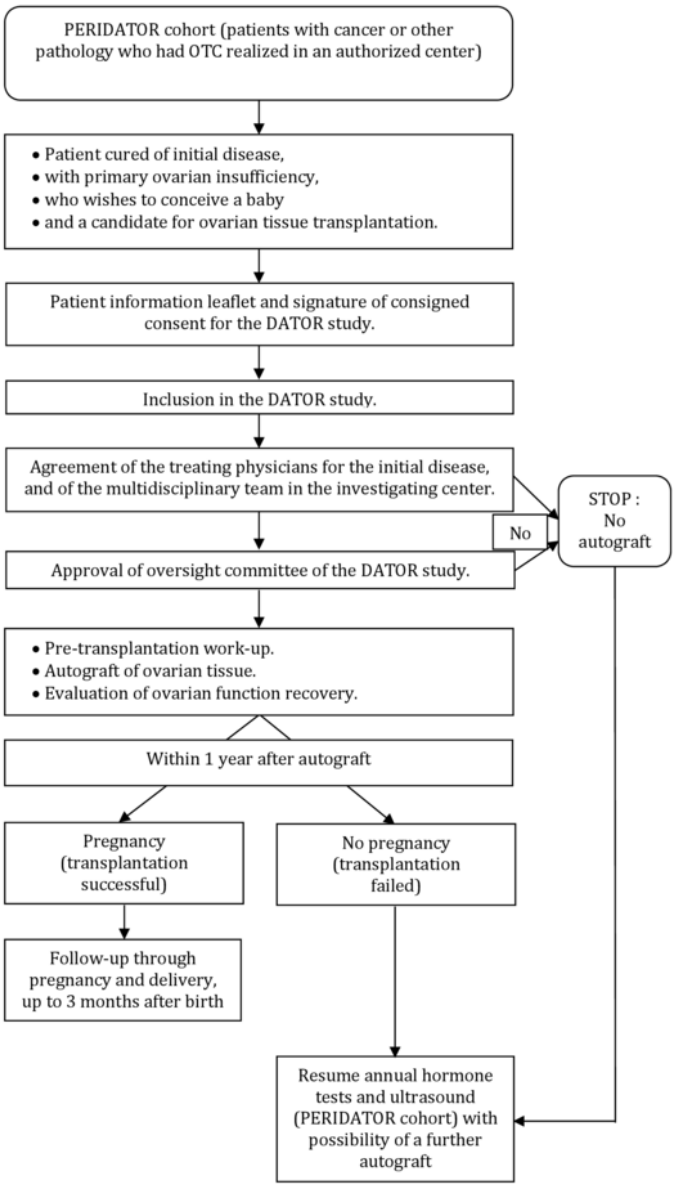
As soon as ovary function is recovered, either by normalization of gonadotropins, with or without elevation of AMH, or by the appearance of echographic signs, monitoring of folliculogenesis and ovulation is implemented at each cycle, with a view to achieving pregnancy by scheduled intercourse, with or without ovulation-stimulating treatment. In case of failure, an appropriate ART technique is implemented (intrauterine insemination or in vitro fertilization with or without intracytoplasmic sperm injection).

Monthly follow-up can be discontinued 1 year after the transplantation if the ovarian function has not recovered. In this case, the transplant is considered to have failed. In this situation, a further transplant attempt with the remaining cryopreserved fragments can be proposed with the approval of the steering committee.

Finally, if the patient becomes pregnant, follow-up is completed by a search for any complications during pregnancy and delivery, and the baby's development is followed up to 3 months after the birth.

The study flowchart is presented in Figure 1.

Figure 1. Study flowchart.



Data Analyzed

Primary Outcome

Patients will be dichotomized into 2 groups. The *restored* group will comprise patients who achieve ovarian function restoration evidenced by the onset of a pregnancy. The *not restored* group will comprise patients who do not achieve ovarian function restoration. Fertility restoration is defined as the occurrence of a pregnancy leading or not leading to a live birth.

Secondary Outcomes

The secondary outcomes are as follows: number of live births after ovarian tissue autograft, number of complications that could result from a surgery with anesthesia or depending on graft quality, number of graft recovery, and number of residual disease development.

The information obtained with this study will contribute to our knowledge on autologous ovarian tissue transplantation, the preservation of ovarian function, and the reuse of self-preserved ovarian tissue to be improved. Advances are also expected in the management of patients.

This protocol will allow the surgical teams of the participating centers to be trained in the practice of the autograft of ovarian cortex, especially the 2-stage grafting technique codified by Limoges' team.

Data Collection and Research Measures

Data pertaining to all patients will be rendered anonymous before being centralized at the coordinating center in Besancon, where they will be verified and completed (if necessary) and entered into a secure database. All study documentation will be conserved in a locked office.

Statistical Methods

An interim analysis was planned on the first 25 patients who arrived at 1 year after transplantation. The objective was to check that the results were sufficiently favorable to allow continuation and extension of the study.

All analyses will be performed using SAS version 9.4 (SAS Institute Inc). Continuous variables will be presented as mean (SD) and median (interquartile range). Categorical variables will be presented as number and percentage.

Some potential prognostic factors will be measured at baseline and will be compared between the *not restored* fertility and *restored* fertility groups using the Pearson chi-square test or Fisher exact test for categorical variables and the Student *t* test or analysis of variance for normally distributed quantitative variables. The Mann-Whitney U and Kruskal-Wallis tests will be used for comparison of nonnormally distributed variables and semiquantitative variables. Multivariate analysis (logistic or Cox regression) will be used if we have a sufficient power for this analysis. A *P* value of less than .05 will be considered statistically significant.

Ethics and Dissemination

This study is conducted in agreement with the Declaration of Helsinki (amended in October 2013). Before study initiation, the protocol and informed consent document were submitted to the ethical review committee of Franche-Comté and to the French National Agency for the Safety of Health Products (*Agence nationale de sécurité des médicaments et des produits de santé*), both of which gave their approval. Signed informed consent is obtained from all participating patients. Patient anonymity is protected by the use of subject identification codes.

Clinical follow-up is provided by physicians and surgeons. The risks associated with ovarian tissue transplantation are the risks related to laparoscopy and general anesthesia. No drugs other than those normally prescribed in daily medical practice are used.

The findings from this study will be disseminated at several regional and international research conferences and as published articles in peer-reviewed journals.

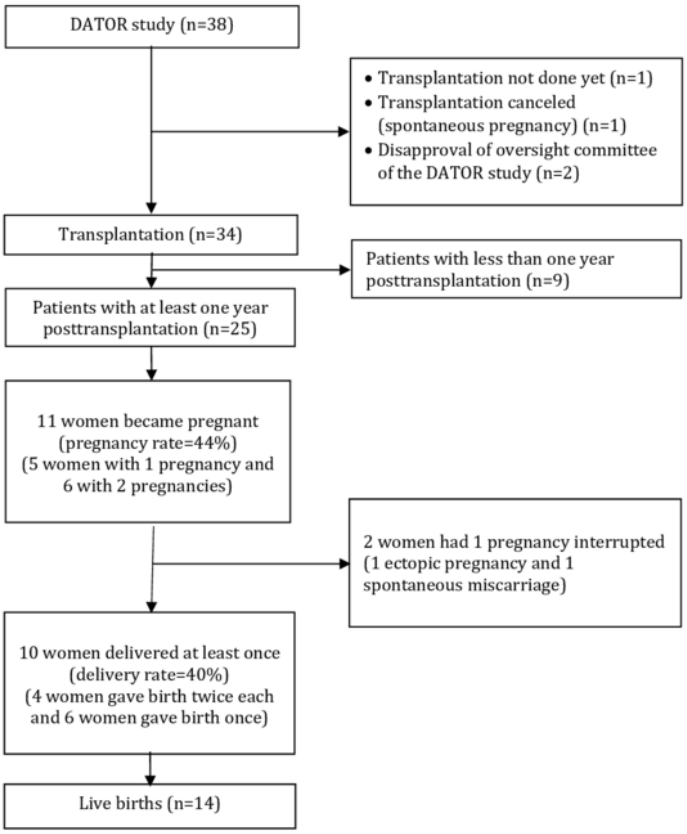
The trial is registered with Clinicaltrials.gov under the number NCT02846064.

Results

Project Progress

Recruitment is ongoing. A total of 142 patients have been included in the PERIDATOR cohort (data as of December 31, 2018), and 38 patients are now cured of the initial disease and have provided written consent to enter the DATOR study. Transplantation has been performed in 34 of them. The flowchart of the preliminary analysis is presented in Figure 2.

Figure 2. Flowchart of the preliminary analysis. DATOR: Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function.



Preliminary Analysis

An interim analysis was planned on the first 25 patients for whom the period of at least 1 year post transplantation was achieved. Among these 25 patients, 11 women succeeded in becoming pregnant (pregnancy rate=44%). In addition, 10 women gave birth to 14 babies, 4 of them conceived twice (delivery rate=40%), and two-third (11/17) of them resulted from natural conception. The average time to conception was 11.3 (SD 6.3) months, with a minimum of 5.7 months and a maximum of 25.5 months.

Patients' characteristics and outcomes of transplantation are presented in Tables 1 and 2. No heterotopic transplantation was performed.

Menses returned spontaneously in 68% of the patients (n=14), on average 5.4 months (SD 2.3) after ovarian tissue autograft (minimum=2, maximum=93; n=22). Antral follicles were found in 20 patients of the 21 patients (95%) for whom data were available. The first antral follicle appeared on average 3.7 months (SD 2.2) after ovarian tissue autograft (minimum=1, maximum=10). From the onset of the first antral follicle in ultrasound, the mean count of antral follicles was 3 (SD 1.6; minimum=1, maximum=8).

The global mean FSH after autotransplantation was 50.1 UI/L (SD 26.7; n=23; minimum=8.2, maximum=133) for all patients, 55 UI/L (SD 32.5; n=14; minimum=8.2, maximum=133) for the *no pregnancy* group and 41 UI/L (SD 9.9; n=9; minimum=32, maximum=65) for the *pregnancy* group, without significant difference. However, a progressive decrease in FSH was observable for the *pregnancy* group at the beginning of the follow-up and more particularly from the third month until falling below the threshold of 20 IU/L on average in the sixth month of follow-up Figure 3.

During the follow-up, AMH was undetectable for 10 patients, detectable for 12, and missing for 3. When positive, on average 3.4 months (SD 0.2) after autograft, the mean level of AMH was 0.3 ng/mL (minimum=0.01, maximum=0.77).

Procedures for the detection and recording of adverse events were implemented. No serious adverse event relating to transplantation and no residual disease reseeding was reported. All babies were born healthy.

Table 1. Demographic and clinical characteristics.

Variables	No pregnancy	Pregnancy	Total	*P* value
Patient, n (%)	14 (56)	11 (44)	25 (100)	N/A[a]
Initial disease, n (%)				
Hodgkin lymphoma	11 (79)	6 (55)	17 (68)	N/A
Non-Hodgkin lymphoma	1 (7)	2 (18)	3 (12)	N/A
Ewing sarcoma	0 (0)	1 (9)	1 (4)	N/A
Periarteritis nodosa	0 (0)	1 (9)	1 (4)	N/A
Systemic mastocytosis	1 (7)	0 (0)	1 (4)	N/A
Sickle cell disease	0 (0)	1 (9)	1 (4)	N/A
Neurolupus	1 (7)	0 (0)	1 (4)	N/A
Gonadotoxic treatment before ovarian tissue cryopreservation, n (%)	12 (67)	6 (33)	18 (100)	.99
Age at cryopreservation (years), mean (SD)	26.2 (4.6)	26.7 (3.8)	26.4 (4.2)	.89
Age at transplantation (years), mean (SD)	33.6 (3.9)	31.6 (4.9)	32.8 (4.3)	.81
Storage duration (years), mean (SD)	6.7 (2.5)	5.9 (3.2)	6.4 (2.8)	.29
Number of grafted fragments, mean (SD)	13 (2.6)	11.6 (4.6)	12 (3)	.56
Follicular density/mm^2, mean (SD)	4.9 (5.2)	5 (5.1)	5 (4.7)	.97
Time to conception (months), mean (SD)	N/A	11.3 (6.3)	N/A	N/A
Follicle-stimulating hormone levels (mUI/mL), mean (SD)	79 (24.8)	86.9 (30.4)	82.5 (27.1)	.43
Anti-Müllerian hormone levels (ng/mL), mean (SD)	0.08 (0.15)	0.03 (0.09)	0.06 (0.13)	.52
Age at conception, mean (SD)	N/A	33.9 (5.2)	N/A	N/A
Live births, n	N/A	14	14	N/A

[a]N/A: not available.

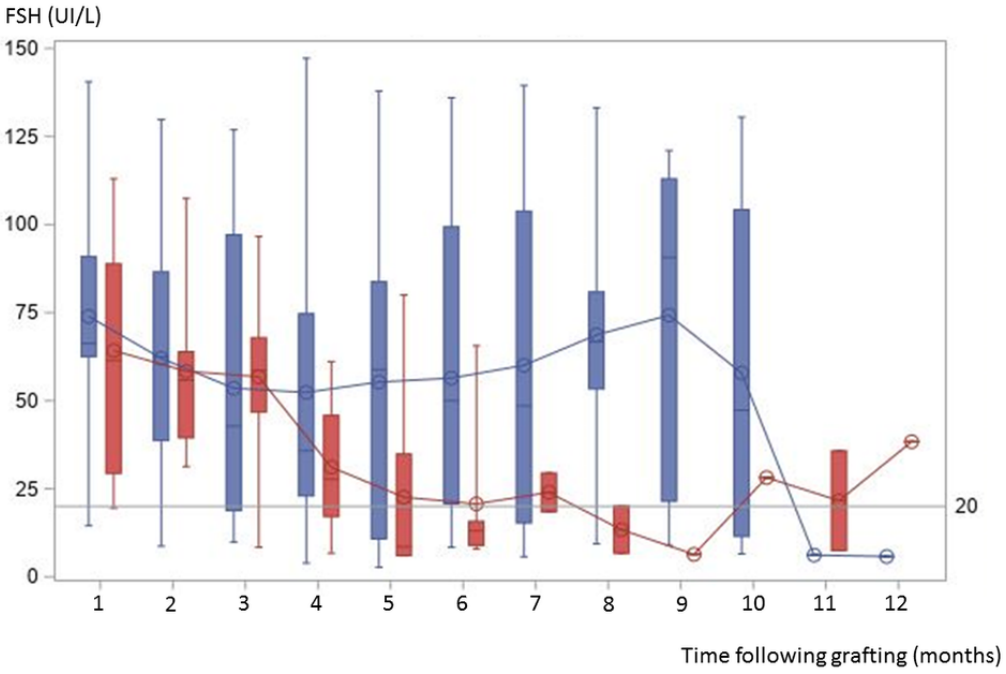
Table 2. Detailed patient characteristics and outcomes of transplantation.

Patient number	Initial disease	Treatment before ovarian tissue cryopreservation	Age at grafting (years)	Assisted reproductive technology	Pregnancy	Weeks of amenorrhea	Outcome	Age at conception (years)
1	Polyarteritis nodosa	Yes	35.6	Yes	Yes	N/A[a]	Ectopic pregnancy	36.8
1	Polyarteritis nodosa	Yes	35.6	Yes	Yes	36.6	Live birth	36.1
2	Sickle cell disease	No	22.5	No	Yes	38	Live birth	27.4
2	Sickle cell disease	No	22.5	No	Yes	36	Live birth	29.8
3	Hodgkin lymphoma	Yes	31.6	Yes	Yes	37.9	Live birth	32.2
4	Hodgkin lymphoma	Yes	26.3	No	Yes	40.1	Live birth	27.7
4	Hodgkin lymphoma	Yes	26.3	No	Yes	40.3	Live birth	30.6
5	Hodgkin lymphoma	Yes	37.9	__[b]	No	N/A	N/A	N/A
6	Hodgkin lymphoma	No	33.2	Yes	No	N/A	—	N/A
7	Non-Hodgkin lymphoma	Yes	31	No	Yes	39	Live birth	33.1
8	Ewing sarcoma	No	32.4	No	Yes	41	Live birth	33.5
8	Ewing sarcoma	No	32.4	No	Yes	40.5	Live birth	—
9	Hodgkin lymphoma	Yes	43	Yes	Yes	N/A	Miscarriage	44.5
10	Non-Hodgkin lymphoma	Yes	30.8	Yes	No	N/A	N/A	N/A
11	Hodgkin lymphoma	Yes	27.6	Yes	No	N/A	N/A	N/A
12	Mastocytosis	No	37.2	Yes	No	N/A	N/A	N/A
13	Hodgkin lymphoma	No	38.9	Yes	No	N/A	N/A	N/A
14	Hodgkin lymphoma	No	37.4	Yes	Yes	38.1	Live birth	38
14	Hodgkin lymphoma	No	37.4	No	Yes	—	Live birth	—
15	Hodgkin lymphoma	Yes	31.3	—	No	N/A	N/A	N/A
16	Hodgkin lymphoma	Yes	27.2	Yes	No	N/A	N/A	N/A
17	Hodgkin lymphoma	Yes	28.8	No	Yes	42	Live Birth	29.4
18	Hodgkin lymphoma	No	30.9	No	Yes	41	Live Birth	31.4
19	Hodgkin lymphoma	Yes	34.7	—	No	N/A	N/A	N/A
20	Neurological lupus	Yes	35.4	—	No	N/A	N/A	N/A
21	Hodgkin lymphoma	No	35.6	No	Yes	41	Live birth	36.5
21	Hodgkin lymphoma	No	35.6	No	Yes	N/A	Ongoing pregnancy	N/A
22	Hodgkin lymphoma	Yes	30.1	Yes	No	N/A	N/A	N/A
23	Hodgkin lymphoma	No	34.1	—	No	N/A	N/A	N/A
24	Hodgkin lymphoma	Yes	34.8	—	No	N/A	N/A	N/A
25	Hodgkin lymphoma	Yes	27.3	—	No	N/A	N/A	N/A

[a]N/A: not appliciable.

[b]Not available.

Figure 3. Box plots of monthly follicle-stimulating hormone levels during the year after autograft for the no pregnancy (blue) and the pregnancy group (red). For each group, the curves represent the monthly follicle-stimulating hormone means for the no pregnancy (blue curve) and for the pregnancy group (red curve), respectively. FSH: follicle-stimulating hormone.



Discussion

Principal Findings

According to the literature, OTC with subsequent autotransplantation provides a natural means of fertility restoration and is the only technique that can be offered to prepubertal girls [68]. For some authors, given the number of live births and ongoing pregnancies described to date, this fertility preservation method may now be considered as established [45,91]. In France, the publication of the decree dated 2008 pertaining to the rules of good clinical and biological practice for medically assisted procreation stipulates that the subsequent use of germinal tissue must remain in the field of research [100]. The publication of the June 30, 2017, decree demands that information on the state of knowledge and the results of any existing research protocols be delivered [90]. In France, the current DATOR study is one of 3 ongoing research protocols enabling the autograft of human ovarian tissue. The DATOR study is a warranty for patients as it enables wider availability of the practice of ovarian cortex autograft, notably the 2-stage grafting technique codified by Dr Pascal Piver (of the team in Limoges), by training the surgical teams in the participating centers. In addition, every case is evaluated by a multidisciplinary team.

The major concern is the reintroduction of the initial disease through malignant cells located in grafted ovarian fragments. In our project, only patients for whom the center's multidisciplinary team and the steering committee give approval are potential candidates for autograft. This agreement takes into account the advancement of techniques evaluating residual disease at the ovarian level.

Furthermore, a study named QUALIGRAFT17 is being carried out in parallel to the DATOR protocol. QUALIGRAFT17 aims to implement complementary analyses to better assess the quality of the grafts and the risk of reintroducing malignant cells. These analyses are performed on fragments of ovarian cortex specifically reserved for the study. A first important result was achieved with the validation of multicolor flow cytometry (MFC) as a method to detect ovarian residual disease in acute lymphoblastic leukemia [96,97]. Hitherto, MFC was a customary method to identify persisting leukemic cells in blood or bone marrow [101]. Our aim is the transfer of this method to other neoplastic pathologies. Another part of this project plans to develop a functional method of qualification consisting of the identification of cells expressing markers of endothelial cells or endothelial progenitors and the assessment of the quality of the stromal cells. This functional qualification and MFC will improve the management of patients for whom risk-free ovarian autograft is possible.

Conclusions

Data on autotransplantation after cryopreservation of ovarian tissue are increasingly encouraging, regarding both its efficacy and its safety. The results produced so far by the DATOR study are in line with such data and thus justify pursuit of this program. Our study will provide important and novel information, especially regarding early development of children born after OTC.

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Conflicts of Interest

None declared.

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Abbreviations

ABM: agence de BioMedecine (BioMedicine agency)
AMH: anti-Müllerian hormone
ART: assisted reproductive technology
DATOR: Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function

FSH: follicle-stimulating hormone
LH: luteinizing hormone
MFC: multicolor flow cytometry
OTC: ovarian tissue cryopreservation
PERIDATOR: Prospective Cohort of Patients Candidates for Ovarian Tissue Autograft

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Original Paper

Quality of Life of Patients With Osteosarcoma in the European American Osteosarcoma Study-1 (EURAMOS-1): Development and Implementation of a Questionnaire Substudy

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Abstract

Background: The quality of life (QoL) of patients with osteosarcoma (OS) may be adversely affected by the disease or its treatment. Therefore, it is important to understand the QoL of patients undergoing treatment for OS to improve the QoL. We report on the first prospective international QoL study that was embedded within a large randomized clinical trial from 4 national study groups.

Objective: This paper aimed to describe the QoL study development, methodology, accrual details, and characteristics of the QoL cohort.

Methods: A total of 2260 patients registered in the EURopean AMerican Osteosarcoma Study-1 (EURAMOS-1), of whom 97.92% (2213/2260) were eligible for the optional QoL assessment and could participate in terms of questionnaire availability. Overall, 61.86% (1369/2213) of patients and/or proxies completed the QoL evaluation at the first assessment time point (E1) after the start of preoperative treatment. The QoL measures used (self- and/or proxy reports) depending on the patient's age and national study group. Participants and nonparticipants in the ancillary QoL study were compared regarding relevant demographic and disease-related characteristics at registration in the trial.

Results: The participation rate at time point E1 did not differ with regard to age, gender, the occurrence of pathological fracture, or the presence of any metastases at diagnosis. No differences were found regarding the primary tumor site. Only the national study group affiliation had an influence on participation. Participation decreased linearly with trial progress up to 20% at the final time point of QoL assessment.

Conclusions: This study demonstrates the feasibility of international cooperation for the purpose of assessing and understanding the QoL of pediatric and adolescent/young adult patients with cancer. Future outcomes of this QoL substudy will help to adapt interventions to improve QoL.

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KEYWORDS

osteosarcoma; quality of life; cancer; child; adolescent; young adult; observational study; sarcoma; survivors of childhood cancer

Introduction

Treatment outcomes for patients diagnosed during adolescence and young adulthood with the most common bone sarcomas, osteosarcoma (OS), and Ewing sarcoma have improved over the past 30 years with the evidence-based introduction of intensive chemotherapy, wide-margin surgery, and, for some, radiation treatment [1-5]. The 5-year survival rate has improved especially for patients aged younger than 25 years [6]. Bone sarcomas and their treatments have a direct impact on organ function, activities of daily life, mobility, and quality of life (QoL), including emotional and physical well-being [5,7,8]. The impact on QoL is a further concern as the majority of patients are diagnosed during adolescence and young adulthood, a crucial time for achieving developmental milestones. As expected, children, adolescents, and young adults diagnosed with bone sarcomas generally report lower levels of health-related quality of life (HRQoL) after surgery compared with the general population, within the domains of physical functioning and overall well-being [8-10]. In addition to physical functioning, patients receiving treatment for a high-grade bone sarcoma also show significantly poorer social functioning [8,10]. This includes lower levels of autonomy and independence when compared with matched healthy peers [8]. The intensive treatment regime as for high-grade bone sarcoma can also compromise QoL [11]. To date, the majority of studies have lacked large sample sizes and standardized treatment and have utilized varying QoL measures [12]. Furthermore, most former studies reported QoL only after surgery; only a few studies conducted prospective assessments from diagnosis to completion of therapy [13], and no study so far has been reported in the setting of a randomized trial.

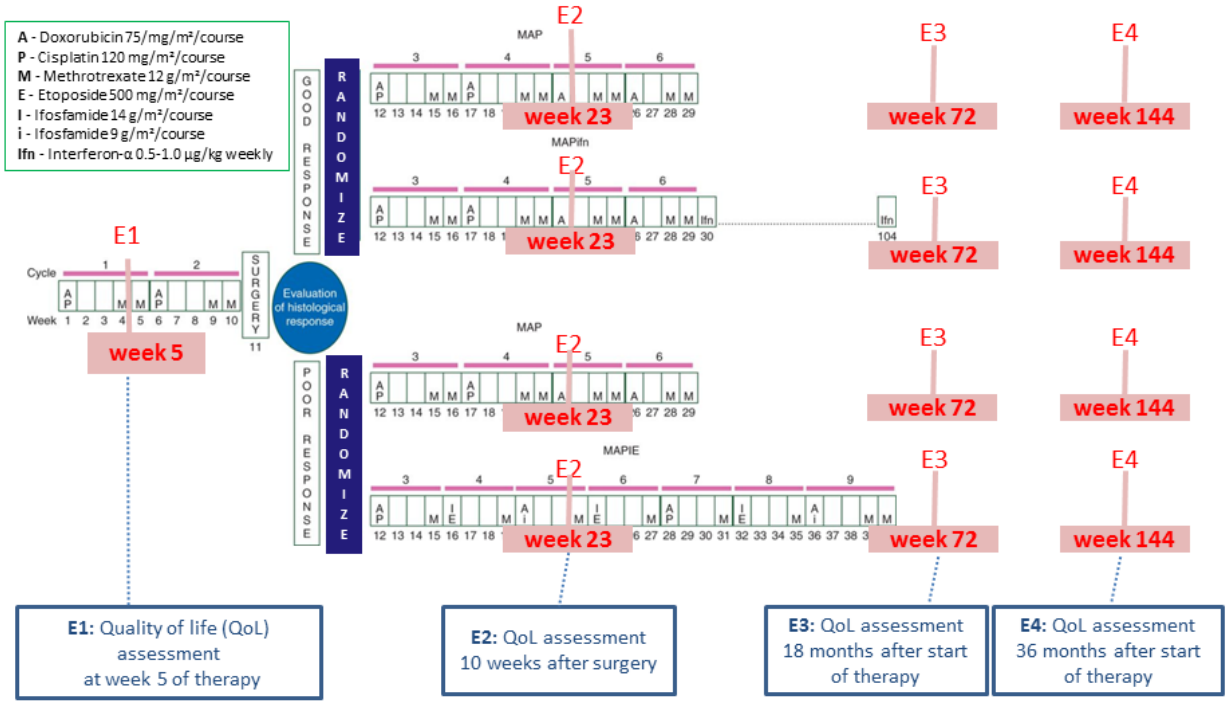
Describing the impact of therapy on QoL from the patients' perspective will lead to a better understanding of the short- and long-term treatment-related side effects and how they can best be managed to improve patient-centered care [12]. In addition, improving QoL during and after bone sarcoma treatment is thought to improve satisfaction and compliance with care and clinician-patient/family communication, which subsequently improves treatment decision [14,15]. Furthermore, through early QoL assessment, undiagnosed psychosocial and physical morbidities can be assessed [15] and potential interventions can be implemented early during treatment. The objective of this study was to assess QoL during and after OS therapy in the context of the EURopean AMerican Osteosarcoma Study-1 (EURAMOS-1). In this paper, we describe the prospective design of the EURAMOS-1 QoL assessment at 4 timepoints, the initial characteristics and participation rates of the study cohort at registration. In addition, we have explained the QoL substudy processes in detail.

Methods

Brief Characteristics and Inclusion Criteria of the European American Osteosarcoma Study-1 Trial

EURAMOS-1 contained 2 randomizations (4 treatment arms) to test treatment strategies for resectable high-grade skeletal OS based on histological response to preoperative chemotherapy (ISRCTN 67613327). The full details are presented elsewhere [16-19]; for an overview on the trial design, see Figure 1. The study recruited patients between 2005 and 2011. Overall, 17 countries from 4 study groups participated in the trial. The participating study groups were the Children's Oncology Group (COG), the Cooperative Osteosarcoma Study (COSS) group, the European Osteosarcoma Intergroup (EOI), and the Scandinavian Sarcoma Group (SSG). All participating countries are listed by study group in Multimedia Appendix 1. QoL was assessed prospectively as a secondary outcome measure in all 4 treatment arms across 4 timepoints during and after treatment.

Figure 1. Timepoints for QoL assessment during treatment in EURopean AMerican Osteosarcoma Study-1 (EURAMOS-1). E1: first assessment timepoint; E2: second assessment timepoint; E3: third assessment timepoint; E4: fourth assessment timepoint; QoL: quality of life.



Inclusion Criteria for Quality-of-Life Assessment Within European American Osteosarcoma Study-1

Patients were eligible for inclusion if the following criteria were fulfilled: diagnosis of previously untreated resectable high-grade OS (any site except craniofacial sites) and they were diagnosed between the ages of 5 years and 40 years.

Questionnaires

No single questionnaire was appropriate for use in all countries for all ages at the time of trial planning. Therefore, the investigators compromised on the use of 1 questionnaire for adults (≥16 years; European Organization for Research and Treatment of Cancer—Quality of Life-Core Questionnaire C30 [EORTC-QLQ-C30]) [20] and 2 age-adapted questionnaires for pediatric patients (self-report and parallelized proxy report): Pediatric Quality of Life Questionnaire (PEDQoL) [21,22] in Central Europe and Scandinavia and Pediatric Quality of Life Inventory (PedsQL) [23,24] in North America and EOI-related countries (eg, United Kingdom or Belgium). QoL assessment was not possible in Hungary, Finland, and the Czech Republic because of a lack of validated translations of the QoL measures as of the time of study development. Wherever possible, the patient completed his/her own questionnaire and a parent filled in a (additional) proxy questionnaire until the patient turned 18 years.

European Organization for Research and Treatment of Cancer—Quality of Life-Core Questionnaire C30

The EORTC-QLQ-C30 is a patient-reported questionnaire that has 8 domains assessing particular aspects significant to adult patients with cancer: 5 functional domains (*Physical*=PF, *Role*=RF, *Cognitive*=CF, *Emotional*=EF, and *Social Function*=SF) and 3 symptom scales (*Fatigue*=FA, *Pain*=PA, and *Nausea and Vomiting*=NV). In addition to these scales, there is a global QoL scale and several single items assessing often-reported symptoms (dyspnoe, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Psychometric properties of the EORTC-QLQ-C30 are proven; the questionnaire is validated cross-culturally in different languages and used in prospective clinical trials in adult patients [25,26]. The EORTC-CLC-Q30 data were divided into 2 age groups (16-17 years and ≥18 years). This allowed us to compare a group that mostly will be treated within a pediatric setting and a group of adult participants.

Pediatric Quality of Life Inventory

The PedsQL is a modular questionnaire instrument designed to measure HRQoL in children and adolescents aged between 2 and 18 years. The 23-item PedsQL 4.0 Generic Core Scale implemented in this study assesses the domains *physical functioning* (8 items), *Emotional Functioning* (5 items), *Social Functioning* (5 items), and *School Functioning* (5 items). In addition, a Psychosocial Health Summary Score can be derived from the questionnaire [23]. A 5-point response scale is utilized across child self-reports for ages 8 to 18 years and parent proxy reports (*0=never a problem* to *4=almost always a problem*). The aggregated reference data of international cohorts (eg, the United States and Great Britain) are available according to the age groups expected in this study [23,27,28].

Pediatric Quality of Life Questionnaire

This cancer-specific questionnaire was developed to assess QoL in children [21,22]. It contains 48 items in which 6 domains can be identified: *Physical Functioning and Pain* (9 questions), *Emotional Functioning* (6 questions), *Body Image* (9 questions), *Social Functioning—Friends and Family* (12 questions), *Cognition* (6 questions), and *Autonomy* (6 questions), as well

as 2 questions about general well-being. Reference data (raw data as well as aggregated data) from unselected German healthy controls are provided according to the age groups expected in this study [22].

Assessment Timepoints

QoL was measured prospectively at 4 timepoints reflecting important therapy milestones. The initial assessment at timepoint 1 (E1) was planned at week 5 after the start of preoperative chemotherapy (±1 week) but before surgical resection. E1 was debated considerably as investigators were interested in pretreatment QoL assessments, but it was recognized that it is difficult to obtain these data before initiation of treatment, and this would result in missing QoL forms for that timepoint. Timepoint 2 (E2) was planned 10 weeks after definitive surgery for a primary tumor (± 2 weeks) as a short-term assessment following surgery. Timepoints 3 (E3) and 4 (E4) were planned 18 and 36 months after the start of therapy (± 1 month), respectively, and were in place to assess long-term outcomes following therapy. An additional timepoint between E2 and E3 was considered, but it was felt to be too burdensome. This prospective assessment across the different treatment arms allows for cross-sectional comparisons (Figure 1) and for changes across time. To include as much information as possible, a few delayed questionnaires were also taken into account for analysis if the questionnaire was received in a comparable treatment period (eg, if timepoint E1 was completed before surgery).

Design, Organization, and Study Structure

The 4 study groups (COG, COSS, EOI, and SSG) established an infrastructure to ensure successful implementation of the EURAMOS-1 trial [19]. Ethical approval for the QoL substudy was obtained in 2005 from the ethical authority of the University Düsseldorf and subsequently in all of the participating study groups. Common data elements were agreed to standardize data collection [19]. The Quality of Life Coordinating Center (QLCC) in Germany was responsible for the QoL data storage and management. German patients returned questionnaires directly to QLCC. For other patients, the institutions sent the completed questionnaires to the national study groups, which transferred them to QLCC by post (SSG and EOI) or electronically (COG; Figure 2).

Figure 2. Logistics of health-related quality of life (HRQoL) assessment during EURopean AMerican Osteosarcoma Study-1 (EURAMOS-1). COG: Children's Oncology Group; COSS: Cooperative Osteosarcoma Study; EOI: European Osteosarcoma Intergroup; QLCC: Quality of Life Coordinating Center; QoL: Quality of Life; SSG: Scandinavian Sarcoma Group.

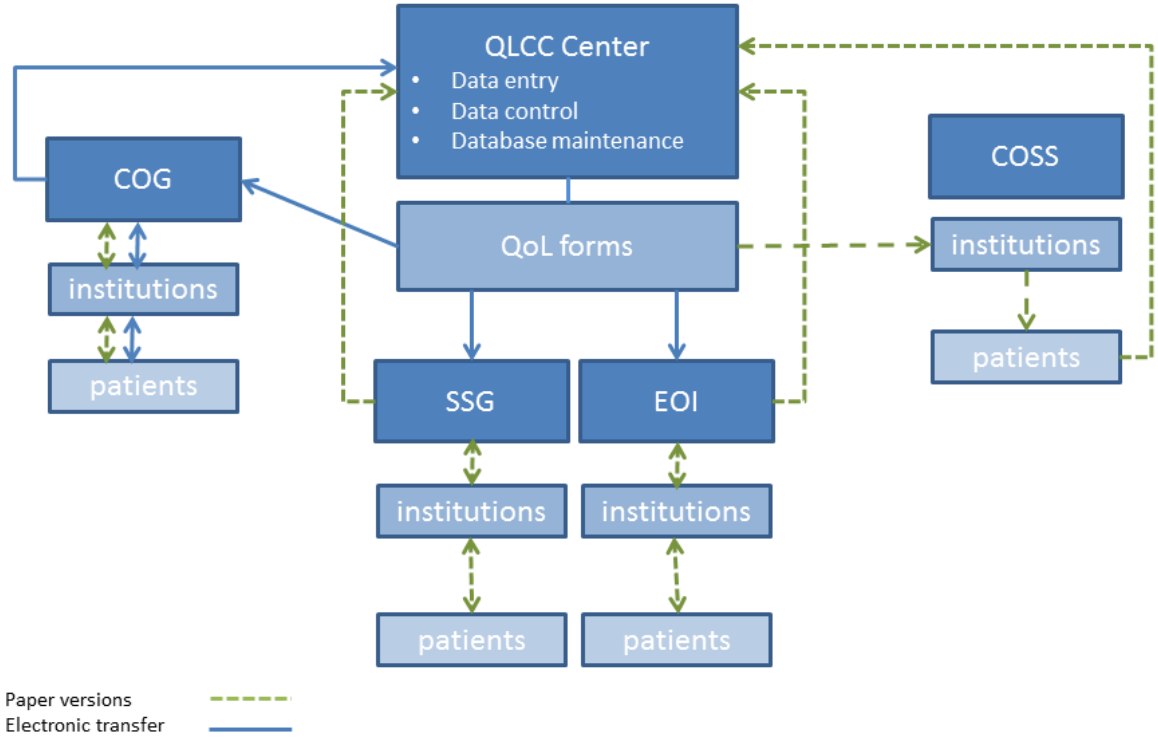


Table 1 shows the questionnaires by age and source of report. Patients' and parents' data were assessed independently and in parallel. QLCC was responsible for data entry, quality control, data base maintenance, and periodic reporting of the status of the QoL substudy. A comprehensive system of error checking was used to detect out-of-range or inconsistent values. If available, errors were compared with any paper records to determine the correct data values if discrepancies were found. The study was open from 2005 to 2011.

Table 1. Quality-of-life questionnaires according to age range and source of report.

Age range and source of report	Quality-of-life questionnaires					
	Pediatric Quality of Life Questionnaire (Calaminus et al [21])		Pediatric Quality of Life Inventory (Varni et al [24])			European Organization for Research and Treatment of Cancer—Quality of Life-Core Questionnaire C30 (Aaronson et al [20])
Age range (years)	≥5-7	≥8-17	≥5-7	≥8-12	>12-17	≥16
Self-reporting	+[a]	+	+	+	+	+
Proxy reporting	+	+	+	+	+	—[b]

[a]Questionnaire used.

[b]Questionnaire not used.

Statistical Analysis

Descriptive analyses were performed for baseline patients' characteristics as well as for the proxy reports. Categorical variables are reported as absolute and relative frequencies. Continuous variables are shown as mean, SD (±), median and range (minimum-maximum). Inferential statistical analyses were performed using Fisher exact tests for categorical variables and nonparametric methods (ie, Mann-Whitney U tests and Kruskal-Wallis tests) for continuous variables.

The comparison between QoL substudy participants and nonparticipants included a multivariable analysis using a logistic regression for modeling the probability for being a *QoL Participant*. The following variables were included in the full model: study (COG [reference category], COSS, EOI, and SSG), age (in years), gender (female vs male [reference category]), lung metastases (no and yes [reference category]), other (nonlung) metastases (no and yes [reference category]), and pathological fracture (no and yes [reference category]). COSS, EOI, and SSG also allowed participants to be defined as having possible metastases (in addition to yes and no), COG did not do so; therefore, all *possible metastases* were classified as *no metastases*.

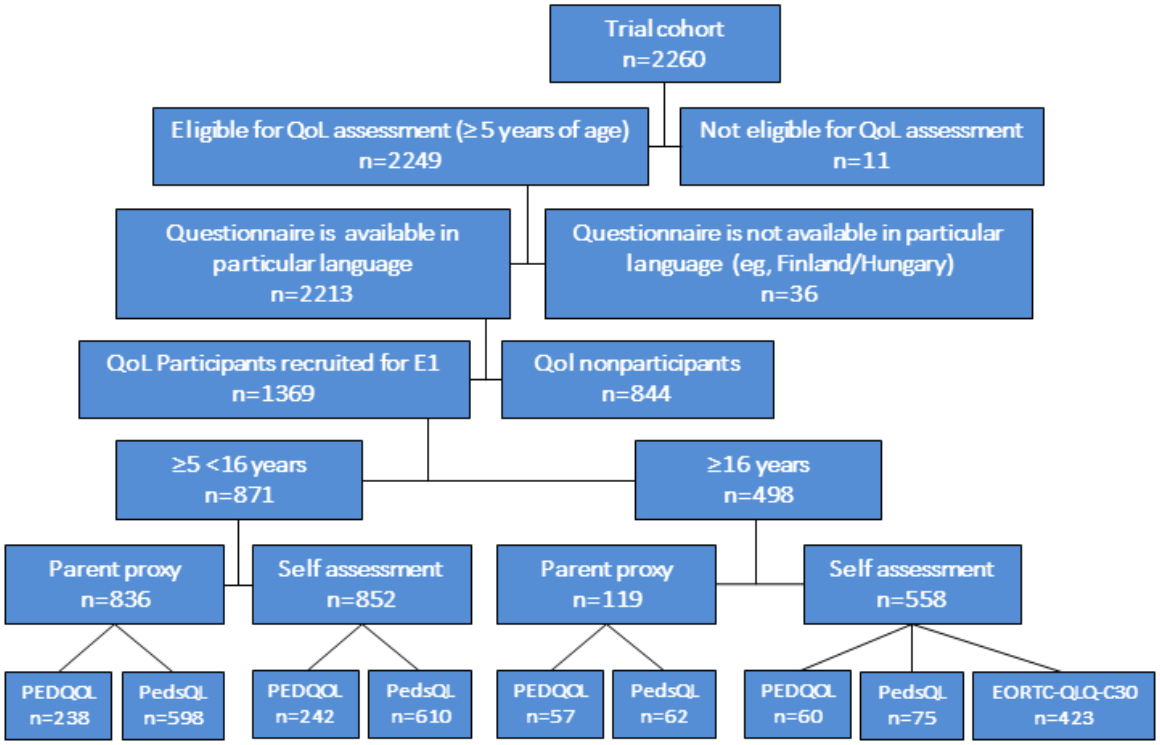
In addition, the logistic regression was calculated for each study group separately. Odds ratios with 95% CI and Wald test *P* values were reported from the full model. Statistical analyses were performed using SAS software, version 9.4 for Windows (SAS Institute). All *P* values and CIs are exploratory without adjustment for multiplicity.

Results

Study Participants at Timepoint E1

The EURAMOS-1 protocol registered 2260 patients who were recruited between April 2005 and June 2011. Among them, 97.92% (2213/2260) were eligible for QoL assessment and could participate in terms of questionnaire availability. For 61.86% (1369/2213) of patients, a QoL evaluation at timepoint E1 before surgery (Figure 3) was available. Nearly one-third (36.38%) of the QoL substudy participants at E1 were aged older than 16 years at timepoint E1 (n=498/1369) and 803/1369 (58.66%) were male. For the pediatric QoL substudy participants aged younger than 16 years (n=871), a completed pediatric self-assessment was available for 852 participants and a completed pediatric parent-proxy assessment was available for 836 participants (for an overview, see Figure 3). In addition, 135 patients older than 16 years filled in a pediatric questionnaire, and so finally, 987 participants with an available pediatric self-assessed questionnaire remained. Of the 987 patients with an available pediatric questionnaire at E1, 302 filled in the PEDQoL version and 685 filled in the PedsQL version (Table 2).

Figure 3. Flowchart regarding quality of life (QoL) eligibility and participation at timepoint E1, split by age and self versus proxy assessment. EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer—Quality of Life-Core Questionnaire C30; PEDQOL: Pediatric Quality of Life; PedsQL: The Pediatric Quality of Life Inventory; E1: first assessment timepoint.



A similar proportion can be found for the parent-proxy assessment. In addition, 423 patients completed the questionnaire for adults (EORTC-QLQ-C30; Table 2).

As patients between 16 and 18 years of age were asked to complete both a pediatric self-assessment and an adult questionnaire according to the compilation of questionnaires agreed before the start of the study, 2 different self-assessment questionnaires are evaluable for one participant. Subsequently, the numbers of questionnaires are higher than the number of participants on the lower part of Figure 3.

Tables 2 and 3 give an overview of patient characteristics, grouped by the availability of self- and proxy reports at timepoint E1. For some patients, a proxy and a self-report are available, for others, only a proxy or a self-report is available; therefore, the numbers on proxy questionnaires are reported separately.

Table 2. Number and characteristics of quality-of-life substudy participants (self-reported) at timepoint 1 (E1) by questionnaire.

Characteristics	Quality-of-life questionnaires		
	Pediatric questionnaires (n=987)		Adult questionnaire (n=423)
	Pediatric Quality of Life Questionnaire (n=302)	Pediatric Quality of Life Inventory (n=685)	European Organization for Research and Treatment of Cancer—Quality of Life-Core Questionnaire C30
Sex (male), n (%)	152 (50.3)	395 (57.7)	292 (69.0)
Age (years)			
≥5-<16, n (%)	242 (80.1)	610 (89.1)	__[a]
≥16, n (%)	60 (19.9)	75 (10.9)	__[b]
16-17	__[b]	__[b]	210 (49.7)
≥18	__[a]	__[a]	213 (50.4)
Overall mean (SD)	13.4 (2.9)	12.8 (2.9)	20.3 (5.2)
Study groups, n (%)			
Children's Oncology Group	0 (0.0)	578 (84.4)	216 (51.0)
Cooperative Osteosarcoma Study Group	182 (60.3)	0 (0.0)	90 (21.3)
European Osteosarcoma Intergroup	56 (18.5)	107 (15.6)	90 (21.3)
Scandinavian Sarcoma Group	64 (21.2)	0 (0.0)	27 (6.4)
Location site, n (%)			
Missing	0 (0.0)	3 (0.4)	4 (1.0)
Upper extremity	30 (9.9)	95 (13.9)	65 (15.4)
Lower extremity	270 (89.4)	584 (85.3)	344 (81.3)
Other	2 (0.7)	3 (0.4)	10 (2.4)
Lung metastases, n (%)			
Missing	0 (0.0)	3 (0.4)	3 (0.7)
Yes	32 (10.6)	99 (14.5)	43 (10.2)
No[c]	270 (89.4)	583 (85.1)	377 (89.1)
Other (nonlung) metastases, n (%)			
Missing	0 (0)	3 (0.4)	3 (0.7)
Yes	12 (4.0)	18 (2.6)	8 (1.9)
No[c]	290 (96.0)	664 (96.9)	412 (97.4)
Pathological fracture at diagnosis, n (%)			
Missing	0 (0)	4 (0.6)	3 (0.7)
No	283 (93.7)	589 (86.0)	375 (88.7)
Yes	19 (6.3)	92 (14.4)	45 (10.6)

[a]Questionnaire not intended for this age group.

[b]Information of this age-category is reported elsewhere in the same table.

[c]*Possible metastases* were combined with *no metastases*.

Table 3. Number and characteristics of quality-of-life substudy participants (proxy report) at registration by questionnaire.

Characteristics	Quality-of-life questionnaires	
	Pediatric Quality of Life Questionnaire (n=295)	Pediatric Quality of Life Inventory (n=660)
Sex (male), n (%)	147 (49.8)	388 (58.8)
Age (years)		
≥5-<16, n (%)	238 (80.7)	598 (90.6)
≥16, n (%)	57 (19.3)	62 (9.4)
Overall mean (SD)	13.0 (2.8)	12.2 (2.9)
Study groups, n (%)		
Children's Oncology Group	N/A[a]	548 (83.0)
Cooperative Osteosarcoma Study group	180 (61.0)	N/A
European Osteosarcoma Intergroup	55 (18.6)	112 (17.0)
Scandinavian Sarcoma Group	60 (20.3)	0 (0.0)

[a]N/A: not applicable.

Participation by Timepoint

Table 4 shows how many patients provided the HRQoL self-report questionnaire, broken down by completed timepoint and all of their combinations during the study. As there were 1369 participants at E1 (Figure 3) and overall there were 1338 patients for timepoint E1, there were 31 participants at timepoint E1 with a proxy report only. The table shows a decreasing linear trend of participation with trial progress, starting with n=1338/2213 (60.46%) self-reports at timepoint 1 and continuing with n=934/2213 (42.21%) at timepoint E2 and n=668/2213(30.19%) and n=450/2213 (20.33%) at timepoints 3 and 4, respectively. However, the largest decline is between timepoint E1 and E2, and accordingly, the highest number of participants with n=454/2213 (20.52%) provided an self-assessment questionnaire at E1 but did not complete a questionnaire at any further timepoint, followed by those group of participants who provided self-assessment questionnaires at all 4 timepoints (273/2213; 12.34%).

Table 5 indicates for how many patients HRQoL proxy assessments were provided, again broken down by each timepoint and all of their combinations. With regard to Table 5, it is important to note that a proxy report was mandatory for child and adolescent patients, including those aged 17 years. Given this subgroup of 1778 patients, n=950/1778 (53.4%) of all parents of these patients provided a proxy report at timepoint E1.

Table 4. Number of patients with available self-assessment at any possible combination of timepoints during study (N=2213).

Timepoints during study				Patients, n (%)
E1[a]	E2[b]	E3[c]	E4[d]	
Yes	Yes	Yes	Yes	273 (12.34)
Yes	Yes	Yes	No	186 (8.40)
Yes	Yes	No	Yes	57 (2.58)
Yes	Yes	No	No	260 (11.75)
Yes	No	Yes	Yes	27 (1.22)
Yes	No	Yes	No	62 (2.80)
Yes	No	No	Yes	19 (0.86)
Yes	No	No	No	454 (20.52)
No	Yes	Yes	Yes	37 (1.67)
No	Yes	Yes	No	42 (1.90)
No	Yes	No	Yes	6 (0.27)
No	Yes	No	No	73 (3.30)
No	No	Yes	Yes	11 (0.50)
No	No	Yes	No	30 (1.36)
No	No	No	Yes	20 (0.90)
No	No	No	No	656 (29.64)

[a]Timepoint 1.

[b]Timepoint 2.

[c]Timepoint 3.

[d]Timepoint 4.

Table 5. Number of patients with an available proxy assessment at any possible combination of timepoints during the study (N=2213).

Timepoints during study				Patients n (%)
E1[a]	E2[b]	E3[c]	E4[d]	
Yes	Yes	Yes	Yes	155 (7.00)
Yes	Yes	Yes	No	159 (7.18)
Yes	Yes	No	Yes	36 (1.63)
Yes	Yes	No	No	223 (10.08)
Yes	No	Yes	Yes	22 (0.99)
Yes	No	Yes	No	36 (1.63)
Yes	No	No	Yes	9 (0.41)
Yes	No	No	No	320 (14.46)
No	Yes	Yes	Yes	19 (0.86)
No	Yes	Yes	No	33 (1.49)
No	Yes	No	Yes	5 (0.23)
No	Yes	No	No	74 (3.34)
No	No	Yes	Yes	9 (0.41)
No	No	Yes	No	17 (0.77)
No	No	No	Yes	8 (0.36)
No	No	No	No	1088 (49.16)

[a]Timepoint 1.

[b]Timepoint 2.

[c]Timepoint 3.

[d]Timepoint 4.

Quality of Life—Nonparticipant Analyses at Timepoint E1

The nonparticipant analyses were performed on patient level if any age-appropriate questionnaire (self- or proxy report or pediatric or adult questionnaire) was available at timepoint E1. Demographic and disease-related characteristics for QoL substudy participants and nonparticipants at timepoint E1 of the QoL study are listed in Table 6. No statistically significant differences in the participation rates with respect to age or gender were seen. Participation rates differed substantially between national study groups (67% COG, 80% SSG, 56% EOI, and 50% COSS). Patients from the COSS group and EOI were less likely to participate in the QoL study's baseline assessment (OR 0.48, 95% CI 0.386-0.600 and OR 0.61, 95% CI 0.482-0.759, respectively) compared with patients from COG, whereas patients from the SSG had a higher participation rate than those from COG (OR 1.97, 95% CI 1.223-3.172).

Table 6. Comparison of quality of life (QoL) nonparticipants and QoL participants at timepoint 1 (E1) in the overall cohort (N=2213).

Characteristics	QoL overall sample at registration	
	QoL nonparticipants (n=844)	QoL participants (n=1369)
Sex (male), n (%)	498 (59.00)	803 (58.66)
Age (years)		
≥5-<16, n (%)	523 (61.97)	871 (63.62)
≥16, n (%)	321 (38.03)	498 (35.94)
Overall mean (SD)	15.4 (5.6)	15.0 (5.10)
Study groups, n (%)		
Children's Oncology Group	380 (45.02)	784 (57.27)
Cooperative Osteosarcoma Study group	242 (28.67)	241 (17.60)
European Osteosarcoma Intergroup	199 (23.58)	252 (18.41)
Scandinavian Sarcoma Group	23 (2.73)	92 (6.72)
Tumor location, n (%)		
Missing	9 (1.07)	7 (0.51)
Upper extremity	130 (15.40)	188 (13.73)
Lower extremity	700 (82.94)	1159 (84.66)
Other	5 (0.59)	15 (1.10)
Lung metastases, n (%)		
Missing	9 (1.07)	6 (0.44)
Yes	125 (14.81)	170 (12.42)
No[a]	710 (84.12)	1193 (87.14)
Other (nonlung) metastases, n (%)		
Missing	11 (1.30)	6 (0.44)
Yes	35 (4.15)	37 (2.70)
No[a]	798 (94.55)	1326 (96.86)
Pathological fracture at diagnosis, n (%)		
Missing	11 (1.30)	7 (0.51)
No	725 (85.90)	1202 (87.80)
Yes	108 (12.80)	160 (11.69)

[a]*Possible metastases* were combined with *no metastases*.

There was no evidence that age (*P*=.27) or gender (*P*=.61) influenced participation. Individual models for each study group revealed that within the COG group, female patients were less likely to participate (OR 0.76, 95% CI 0.585-0.974; *P*=.03), whereas female patients were more likely to participate within the COSS group (OR 1.57, 95% CI 1.070-2.29; *P*=.02). For the EOI and the SSG, gender did not have an influence on the participation.

Considering participation rates at timepoint E1 with regard to disease characteristics, no differences in participation were obtained with regard to major tumor site (*P*=.29), occurrence of pathological fracture at diagnosis (*P*=.13), and initial presentation with metastasis (lung; *P*=.10), or other sites (*P*=.13) before registration. Patients with femur as the primary site contributed most frequently to the baseline QoL assessments (695; 51.0%), whereas patients with radius as the primary site participated relatively less frequently (16; 1.2%).

Discussion

Principal Findings

Here, we describe the QoL substudy embedded in the international OS trial, EURAMOS-1. A total of 4 national study groups that included 17 countries contributed to the study and resulted in the first prospective QoL international study of OS. We collected at least at timepoint E1 QoL information from nearly 1400 patients with an age range from 5 to 40 years. Most reported OS QoL studies were smaller and/or have focused only on posttreatment or were not prospective from the time of diagnosis [8-10]. This prospective study aimed to provide

information not previously reported in the literature and results will help to develop interventions to improve QoL.

Overall, in EURAMOS-1, there were no differences in participation rates at timepoint E1 with regard to the age, gender, site of primary tumor involvement, occurrence of pathological fracture, or occurrence of lung or other metastases at diagnosis between QoL substudy participants and nonparticipants. However, a difference of participation rates between the different national study groups was evident. Logistic regression revealed that patients from the COG were more likely to participate in the QoL assessment compared with COSS and EOI patients, but they were less likely to participate compared with patients from the SSG. In addition, within national study groups (COSS and COG), some significant differences in gender participation were seen. Beside differences in the national study group structure, cultural tendencies could have influenced the different response rates. Further investigation into these differences is warranted.

Comparison With Previous Work

Although there was a participation rate of about 60% at timepoint E1 and the participation rates regarding self-assessment decreased to just over 20% at timepoint E4, this is reasonable given the characteristics of the study cohort (eg, in terms of participant's age range and the number of countries involved). In other HRQoL studies involving children with cancer, the response rates have varied between 58% and 98% [29]. A recent multicenter prospective study including children with lymphoblastic leukemia reported a participation rate of 63% and obtained also a less pronounced but substantial linear decline of participation with study progress [30]. One must keep in mind that investigating QoL in adolescents and young adults (AYAs) may be even more difficult (in this study, 56.5% were aged ≥13 years) because of their developmental status and pursuit of autonomy. These circumstances probably influenced the participation rates. In addition, declining participation rates over the course of the trial are also influenced by overall and event-free survival (eg, at 36 months after biopsy, they were approximately 80% and 60%, respectively) [31]. Rosenberg's study [32] of only AYA patients reported a response rate of only 74% at a single timepoint, even when patients were rewarded for participation. There are no comparable sarcoma trials that include QoL and cover such a broad study age range from various countries and ethnicities. Compared with other international QoL substudies in adult cancer RCTs, these studies obtained higher participation rates at baseline in different diagnoses, for example, leukemia [33] or ovarian cancer [34,35]. However, these trials differed also in terms of assessment method. For instance, provision of an electronic device may have increased the likelihood of participating in the study by Topp et al [33]. Moreover, only adult but no adolescent patients were included. In the future, this could be improved by incorporating Web-based or mobile apps, according to the recommendation by Johnston et al [29] who explored reasons for nonparticipation in QoL studies on children with cancer and their parents. They came to the conclusion that this may address many logistical challenges.

Limitations

Some limitations have to be addressed. We did not assess the level of baseline pain or the extent of anxiety regarding the diagnosis or the urgency to start treatment; both variables may have an important influence on participation rate. Large sample sizes increase the chance of obtaining significant results. Therefore, our results have to be interpreted cautiously. The unavailability of a common QoL questionnaire usable across all groups/countries is a limitation in comparison across groups but was unavoidable. Given the large number of participating sites, how the questionnaires were provided to families and administered may lead to differences. This prospective design does allow analysis of changes over time and at an intraindividual level; however, the representativeness of the collected data may be affected by low participation rates (particularly in respect to the reduced sample size at timepoint E4). In addition, the comparability of measurements is limited as the questionnaires changed (at the age of 16 years) between timepoints and differed between national study groups; participants could also choose to participate only at certain timepoints. To overcome this obstacle, we plan on using a linking method for score conversion [36] for the subscales with sufficient conceptual overlap between questionnaires. We will base the linking of scores on a subset of participants who completed 2 questionnaires at the same timepoint (*single-group design*) according to schedule. We will assess concordance using appropriate measures (eg, Bland-Altman plots and Lin correlation concordance coefficient) [37,38].

Conclusions

Despite some of the limitations, this is largest prospective assessment of QoL in OS therapy. Further analyses will be able to look at prospective changes and be able to look at long-term outcomes and differences between different demographic groups. This study also highlights the ability of clinicians and researchers to work together to perform large QoL investigations across different national study groups. For such an endeavor to succeed, there needed to support from each national study group that includes first recognizing the importance of QoL assessments, the provision of infrastructure for the collection and management of QoL data, the identification of *lead* QoL investigators for each group, and time/support for meeting as a group. Through the initial phases of the development of this study, we needed to come together to identify the most appropriate QoL questionnaires that were available at the time that it was validated for the different involved countries/languages, had similar domains, and can span the age range of participants. We then had to determine how often and when assessments will be done while accounting for structural differences in the various groups/countries in how they delivered therapy and administered questionnaires and ensuring that questionnaires were not too burdensome. After intensive discussions, compromises were made regarding the timing of initial QoL assessment and the number of assessments. In terms of administration, it was decided that the administration and tracking of the assessments has to be in the hands of the national study groups and that centralized administration would not be possible. However, the data management and quality control checks were centralized with the QLCC taking the lead. Each

national study group determined its own system of transferring the QoL forms/data to the QLCC. Overall, this was a successful endeavor, and we hope learnings from this partnership will lead to future studies. With this study, future analyses will lead to a better understanding of the impact OS therapy has on QoL and how patient and particular disease characteristics influence QoL in the short and long term and how QoL changes over time. This will help to ameliorate or prevent the potential decline in psychosocial and physical morbidities of patients undergoing OS treatment.

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- Netherlands: ZonMw (Council for Medical Research)

- Norway: Research Council of Norway

- Sweden: SSG and Swedish Childhood Cancer Fund

- Switzerland: Swiss Paediatric Oncology Group

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Conflicts of Interest

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NM reports employment by Five Prime Therapeutics, Inc, outside the submitted work.
The remaining authors declare no conflicts of interest.

Multimedia Appendix 1
Participating countries listed by study group.

[PDF File (Adobe PDF File), 14 KB - resprot_v8i9e14406_app1.pdf]

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Abbreviations

AYA: adolescents and young adults
COG: Children's Oncology Group
COSS: Cooperative Osteosarcoma Study
EOI: European Osteosarcoma Intergroup
EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer—Quality of Life-Core Questionnaire C30
EURAMOS-1: EURopean AMerican Osteosarcoma Study-1
HRQoL: health-related quality of life
NCTN: National Clinical Trial Network
OS: osteosarcoma
QLCC: Quality of Life Coordinating Center
QoL: quality of life
SSG: Scandinavian Sarcoma Group

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Corrigenda and Addenda

Update on Schnelle et al and Expression of Editorial Concern

JMIR Editorial Office

Related Articles:

Correction of: https://www.researchprotocols.org/2017/11/e234/

Correction of: https://publichealth.jmir.org/2018/1/e6/

Correction of: https://www.researchprotocols.org/2018/5/e10469/

Correction of: https://publichealth.jmir.org/2018/2/e53/

(JMIR Res Protoc 2019;8(9):e16313) doi:10.2196/16313

Background

The Office of the Deputy Vice-Chancellor at the University of Queensland (UQ) has concluded its research misconduct investigation regarding the two papers, hereafter referred to as Paper 1 (the protocol in JMIR Research Protocols) [1] and Paper 2 (the results in JMIR Public Health and Surveillance) [2]. In short, the main findings were that no retraction is required.

There were issues with inadequate disclosure of conflict of interests on submission, as well as "honest" mistakes, both of which were fully addressed in the JMIR Expression of Editorial Concern, Correction of Conflict of Interest and Affiliation, and Data Corrections, which we published in both affected journals [3,4] in close consultation with the Committee on Publication Ethics (COPE), together with the updated conflict of interest statement and data corrections submitted by the authors. According to the Council of Science Editors (CSE), the purpose of an Expression of Editorial Concern is to draw attention to potential problems in a publication, "but it does not go so far as to retract or correct an article." CSE continues that "an editor who has a significant concern about the reliability of an article but not enough information to warrant a retraction until an institutional investigation is complete will sometimes use an expression of concern" [5]. COPE's guidelines encourage editors to consider an Expression of Editorial Concern if "they receive inconclusive evidence of research or publication misconduct by the authors" or if "an investigation is underway but a judgement will not be available for a considerable time" [6], which both fit the circumstances of this case.

Response

As the University of Queensland investigation is now complete, we are updating the Expression of Editorial Concern following the key findings of the university report, from which we cite below, together with our response, as follows:

University of Queensland:

> *The investigation established that a number of authors of the above-named publications have associations with Universal Medicine. The investigation found that the conflict of interest statements submitted with the papers, which were not subsequently published by JMIR, indicate that there is a potential for a conflict of interest but do not adequately declare the nature of the authors' associations with Universal Medicine. Those associations were subsequently adequately detailed in the updated conflict of interest statement by the authors published in the JMIR Expression of Editorial Concern, Correction of Conflict of Interest and Affiliation, and Data Corrections (doi:10.2196/publichealth.9932).*

JMIR response: The investigation confirms our concerns that the vaguely phrased originally submitted COI (disclosing that the authors are "insiders") did "not adequately declare the nature of the authors' associations with Universal Medicine". No changes to the Expressions of Editorial Concern or corrections are deemed necessary because they point out exactly that concern. JMIR may not have accepted the papers if the editor and reviewers had been aware of the full extent of the authors' COIs, or at least would have insisted on describing ways to manage the significant COIs of the authors.

University of Queensland:

> *In relation to the concern about statistical errors in Paper 2, the authors submitted a correction to JMIR prior to the University becoming aware of the concerns. In this instance the authors acted to correct the error as soon as possible after becoming aware of it. There is no evidence that these were more than honest mistakes. The errors were corrected in the JMIR Expression of Editorial Concern, Correction of Conflict of Interest and Affiliation, and Data Corrections (doi:10.2196/publichealth.9932)"*

JMIR response: To reflect the UQ judgement that "there is no evidence that these were more than honest mistakes" we have

updated the Expressions of Editorial Concern [3,4] to remove the following paragraph:

> *Finally, we are very concerned that the original results paper contained large statistical errors inflating the effect sizes (now corrected, see data correction below), which the authors themselves corrected (see below). We are giving the authors the benefit of the doubt in assuming that these were honest mistakes and not intentional errors, but it casts further doubts on the level of oversight as well as vetting of the data by an independent person.*

University of Queensland:

> *The investigation determined that there are errors in the language used to describe the status of the study in Paper 1. Specifically, Paper 1 describes a planned study as if it had not begun, but at the time of publication data collection had been completed. The investigation found that the inaccuracy in reporting of the study status represents an inadvertent error. Nonetheless, the language used may give an inaccurate impression of the study status that requires correcting.*

JMIR response: We have inserted the phrase "At the time of publication of this protocol, data collection has been completed" in the Methods section of the abstract and body of the protocol paper (Paper 1 [1]). In addition, we have added an IRRID (International Registered Report Identifier) to both papers [1,2], which indicate (through the prefix DE for "Data Existing") that the data were already collected at the time as is now standard practice for all protocols we publish [7].

The correction will appear in the online version of the papers on the JMIR website on September 23, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected articles have also been resubmitted to those repositories.

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Abbreviations

CSE: Council of Science Editors
COPE: Committee on Publication Ethics
UQ: University of Queensland

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Corrigenda and Addenda

Authorship Correction: Promising Approaches for Engaging Youth and Young Adults Living with HIV in HIV Primary Care Using Social Media and Mobile Technology Interventions: Protocol for the SPNS Social Media Initiative

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Related Article:

Correction of: https://www.researchprotocols.org/2019/1/e10681

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The authors of "Promising Approaches for Engaging Youth and Young Adults Living with HIV in HIV Primary Care Using Social Media and Mobile Technology Interventions: Protocol for the SPNS Social Media Initiative" (JMIR Res Protoc 2019;8(1):e10681) have added the Special Projects of National Significance Social Media Initiative Study Group as a group author on the original publication in last position. The new list of authors is as follows:

Melissa Medich, Dallas T Swendeman, W Scott Comulada, Uyen H Kao, Janet J Myers, Ronald A Brooks, Special Projects of National Significance Social Media Initiative Study Group

The corrections will appear in the online version of the paper on the JMIR website on September 9, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article, including collaborators associated with the group author, also has been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Evaluating the Long-Term Effectiveness of School-Based Depression, Anxiety, and Substance Use Prevention Into Young Adulthood: Protocol for the Climate School Combined Study

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During recruitment for the current phase of the study, the authors of "Evaluating the Long-Term Effectiveness of School-Based Depression, Anxiety, and Substance Use Prevention Into Young Adulthood: Protocol for the Climate School Combined Study" (JMIR Res Protoc 2018;7(11):e11372) discovered that the participant database contained 25 duplicate records.

These 25 records represented cases where the same participant had been able to create two separate accounts on the website where participant data was recorded and managed. The correct sample size for the original phase of the study is 6386, rather than 6411, after removing these duplicates.

Accordingly, the following changes have been made:

Abstract

- Under "Methods" in the sentence beginning "A cluster randomized controlled trial (the CSC study) was conducted with 6411 participants", the number of participants has been changed from 6411 to 6386.

Introduction

- In the subsection "The Climate School Combined Study: First Randomized Controlled Trial of Simultaneous Universal Prevention for Anxiety, Depression, and Substance Misuse" in the sentence "A total of 71 schools and 6411 students aged 13 to 14 years at baseline participated in the trial", the number of students has been changed from 6411 to 6386.

Methods

- In the subsection "Ethical Approval and Consent to Participate", the sentence "The study was approved by the University of New South Wales Human Research Ethics Committee, Australia (HC13073)" has been changed to "The study was approved by the University of Sydney Human Research Ethics Committee, Australia (2018/906)".
- In the subsection "Study Design", the sentence "The final cohort at baseline consisted of 6411 year 8 students from 71 schools (mean age 13.5 years [SD 0.6], 54.78% 3511/6411) female, 81.25% [5209/6411] born in Australia)" has been changed to "The final cohort at baseline consisted of 6386 year 8 students from 71 schools (mean age 13.5 years [SD 0.6], 54.84% [3502/6386] female, 81.24% [5188/6386] born in Australia)."
- In the subsection "Sample Size Calculations" in the sentence "Participants for this study come from 6411 students from 71 schools recruited to the original CSC study", 6411 has been corrected to 6386. In the sentence "In our original study, we achieved a total sample size of 6411 students", 6411 has been corrected to 6386.

Discussion

- In the subsection "Strengths and Limitations" in the sentence beginning "Although follow-up rates for the original CSC study remained relatively high across survey waves (ranging from 66% to 88%)", 66% has been corrected to 67%.

Multimedia Appendices

- Both multimedia appendices have been updated to reflect the correct number of participants followed up at each occasion.

The corrections will appear in the online version of the paper on the JMIR website on September 26, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article also has been resubmitted to those repositories.

Multimedia Appendix 1
Consort diagram of the Climate Schools Combined study.
[PDF File (Adobe PDF File), 101KB - resprot_v8i9e15391_app1.pdf]

Multimedia Appendix 2
Completed Climate Schools Combined (CSC) Study assessments and timeline for extended follow-up assessments.
[PDF File (Adobe PDF File), 113KB - resprot_v8i9e15391_app2.pdf]

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