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Design and Rationale of the National Observational Multicentric Tunisian Registry of Hypertension: Protocol for Evaluating Hypertensive Patient Care in Clinical Practice

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Abstract

Background: This study was designed to evaluate the care of hypertensive patients in daily clinical practice in public and private centers in all Tunisian regions.

Objective: This study will provide us an overview of hypertension (HTN) management in Tunisia and the degree of adherence of practitioners to international recommendations.

Methods: This is a national observational cross-sectional multicenter study that will include patients older than 18 years with HTN for a duration of 4 weeks, managed in the public sector from primary and secondary care centers as well as patients managed in the private sector. Every participating patient signed a consent form. The study will exclude patients undergoing dialysis. The parameters that will be evaluated are demographic and anthropometric data, lifestyle habits, blood pressure levels, lipid profiles, treatment, and adherence to treatment. The data are collected via the web interface in the Dacima Clinical Suite.

Results: The study began on April 15, 2019 and ended on May 15, 2019. During this period, we included 25,890 patients with HTN. Data collection involved 321 investigators from 24 Tunisian districts. The investigators were doctors working in the private and public sectors.

Conclusions: Observational studies are extremely useful in improving the management of HTN in developing countries.

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KEYWORDS

National Tunisian Registry; hypertension

Introduction

Hypertension (HTN) is widespread in many developing and developed countries [1]. According to a 2010 report by the Institute of Medicine, HTN is a neglected disease, often ignored by the general public and underestimated by the medical world [2].

However, more than a quarter of the world's adult population is already hypertensive, and this number is expected to increase to 1.56 billion by 2025 [3,4]. Unfortunately, HTN causes more than 7 million premature deaths a year and contributes to 4.5% of the global disease burden [5,6]. HTN is also a risk factor for cardiovascular diseases responsible for 30% of all deaths worldwide, which can be controlled [7,8].

Many clinical trials have shown that stringent blood pressure (BP) control can significantly reduce cardiovascular risk [9,10] and certain sequelae such as stroke, myocardial infarction, sudden cardiac arrest, peripheral vascular disease, and renal insufficiency [11-13].

HTN in Tunisia is a public health issue considering its current frequency [14-16]. As no relevant updated data exist, this work presents a new relational database to obtain an overview of the management of hypertensive patients in Tunisia and enable adequate protection planning. Therefore, a multicenter observatory focusing on the demographic, anthropometric, and therapeutic features of HTN in Tunisia is mandatory. The collected data will allow us to assimilate our practices and know the degree of adherence by practitioners to international recommendations for this pathology treatment.

The aim of the National Tunisian Registry of Hypertension (NATURE-HTN) is to describe the epidemiological profile of HTN in Tunisia, determine the cardiovascular risk level of Tunisian hypertensive patients, and obtain an idea about the percentage of patients treated for therapeutic purposes.

Methods

Several secondary end points are defined, such as evaluating the therapeutic adequacy with respect to that specified in the international recommendations of the European Society of Hypertension-European Society of Cardiology (ESH-ESC) 2018 for managing HTN and evaluating the degree of therapeutic inertia.

Study Design and Patient Enrollment

A national observatory, longitudinal, and multicentric register study was carried out over a month, without clinical follow-up and investigations. We included patients managed in the private and public sectors as well as from primary and secondary care centers.

During office visits, we included patients above 18 years with known or newly diagnosed elevated BP after signing a consent form. Except for severe HT (eg, grade 3 and especially high-risk patients), the new HT diagnosis was confirmed according to the ESC and ESH guidelines as either out-of-office BP measurements above the recommended thresholds or repeated office BP measurements above 140 mmHg for the systolic blood pressure (SBP) and 90 mmHg for the diastolic blood pressure (DBP) during more than 1 visit [11].

Exclusion Criteria

We excluded patients undergoing hemodialysis, pregnant women, individuals classified as white-coat HT patients, and patients who refused to sign the consent form from the study.

During the office visit, the physician had to complete the case report form of the registry after patient interrogation and examination. Information on sociodemographic characteristics including age, gender, education level, health insurance, smoking, diabetes, pulmonary diseases, hypothyroidism, moderate renal failure history defined by an MDRD (Modification of Diet in Renal Disease) creatinine clearance <60 mL/min, coronary disease, and history of stroke were collected.

The interview included questions related to drug compliance and salt intake as well as sport practice. Physical activity was considered regular when it was performed at least 30 minutes 3 times a week. During physical examination, we measured the weight and height to assess the BMI (BMI= weight/[height]^2). Obesity is operationally defined as a BMI exceeding 30 kg/m^2 and is subclassified into moderate (BMI=30-34.9), morbid (BMI=35-39.9), and severe (BMI≥40). BP measurements were conducted using a standardized auscultatory or oscillometric sphygmomanometer after at least 15 min of rest. We recorded 2 separate measurements at least 3 minutes apart and considered the mean of the 2 measurements. In patients with asymmetric BP between the 2 arms, we considered the higher pressure.

We confirmed whether the patients had a sinus rhythm or atrial fibrillation through electrocardiograms and searched for left ventricle hypertrophy (LVH) based on the definition recommended by the ESC/ESH guidelines (Sokolow-Lyon index>35 mm or R in a VL≥11 mm) [11]. We searched for LVH in echocardiographic findings as well (if the patients underwent echocardiography during the last year).

We also recorded the biological tests performed during the last 6 months before the office visit, especially creatinine, glycaemia, cholesterol, kaliemia, and microalbuminuria (if performed during the last year).

To assess and control BP, we evaluated only patients diagnosed with HTN for more than 6 months. The primary end point in our study was the rate of HTN control. Uncontrolled HTN was defined according to the ESC/ESH guidelines as an average SBP above 140 mmHg and an average DBP above 90 mmHg [11].

Ethics Consideration

The study protocol, the consent form prepared by the steering committee, and the creation of the registry were approved by the ethic committee of the Hospital of the Internal Security Forces. Patients must give their consent before being included in the registry.The steering committee will check for any violation of the protocol by the investigators (inclusion of patients who are not eligible according to selection criteria) and will make a decision on the exclusion of the concerned patient(s).

Sample Size and Data Collection

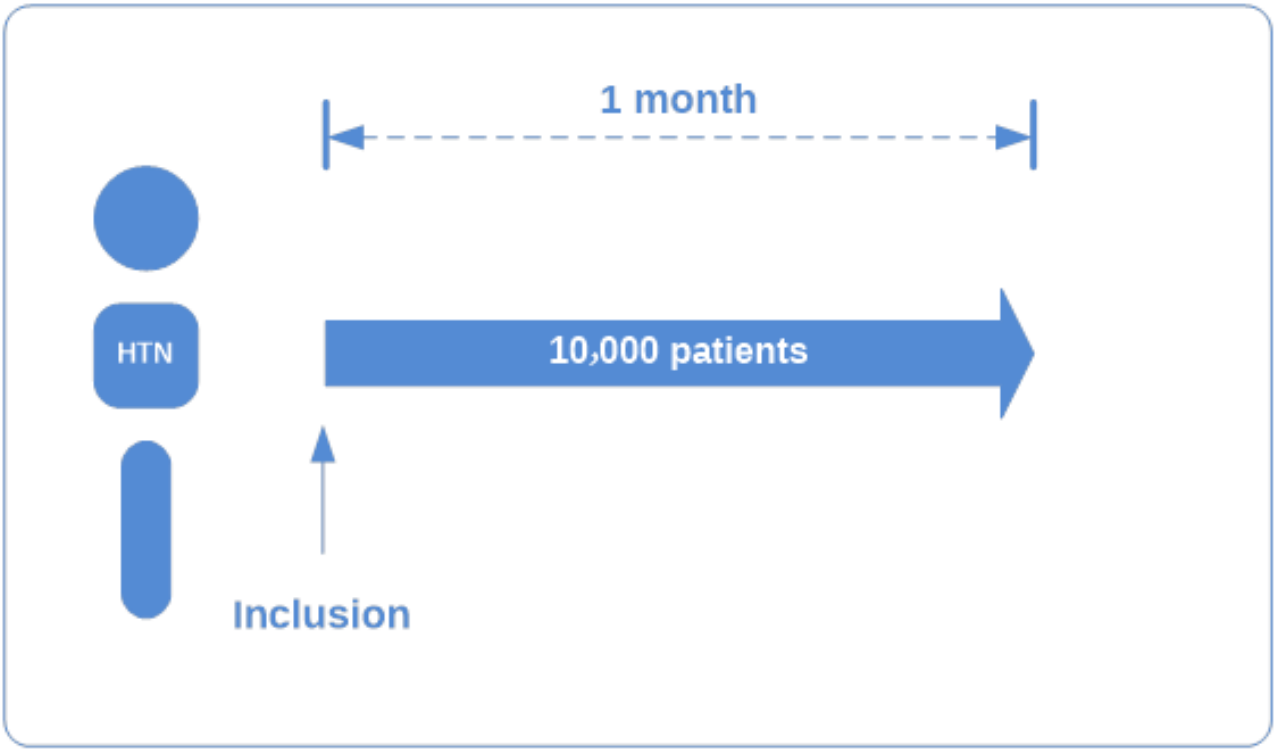
Eligible patients according to the inclusion and exclusion criteria were selected by more than 600 investigators (working in the public and private sectors) specialized in cardiology, nephrology, endocrinology, internal medicine, and general medicine.

The target simple size of the whole study was calculated using the following formula: $N = Z^2 \times p0 \times (1 - p0)/i^2$ (Z=1.96 if we consider a confidence level of 95%, and p0=24.1%; it corresponds to the control rate of HTN in the TAHINA project). More than 7000 patients were needed.

Patients were included continuously until the end of the inclusion period. The inclusion lasted for 1 month without any follow-up, as shown in Figure 1. Given the observational nature of the NATURE-HTN study, no specific treatment or intervention is planned for HTN management. Patients should be cared for according to their usual medical habits.

The data were collected via the web interface in the Dacima Clinical Suite (Dacima Software Inc). The electronic data capture platform complies with the following international standards: Food and Drug Administration 21 Code of Federal Regulations part 11, Health Insurance Portability and Accountability Act, and International Conference on Harmonization.

Figure 1. Protocol of population inclusion. HTN: hypertension.



Statistical Analysis

The Dacima Clinical Suite platform enables the collection of data through the web interface and their extraction in the SAS or SPSS format. The statistical analysis is exploratory, involving the calculation of the 95% CI.

The data will be described for the entire population of interest. Statistical tests will be bilateral with a statistical significance threshold of 5%. ANOVA will be performed for the quantitative variables according to their normal distribution (parametric tests for the variables that follow a normal distribution and nonparametric tests in the other cases). A chi-square test will be performed for the categorical variables (or corrected for continuity if the validity conditions for the chi-square test are not met, namely if the theoretical number is less than 5).

The data review committee is composed of the coordinators of the steering committee of the study as well independent experts in data management. The purpose of the data review committee is to manage data queries and validate the final statistical analysis plan. The committee will also be responsible for validating subsequent publications that will be conducted.

The protocol of the NATURE-HTN registry has been approved by the Tunisian Society of Cardiology and Cardiovascular Surgery. The NATURE-HTN study has been submitted to ClinicalTrials.gov and registered under the identifier NCT04013503.

The NATURE-HTN registry does not impose any specific intervention. Treatments of the patients follow the usual recommendations for managing HTN. Clinical events occurring during the study are not to be recorded.

Study Sponsorship

The NATURE-HTN registry study is sponsored by the Tunisian Society of Cardiology and Cardiovascular Surgery.

Results

The study began on April 15, 2019 and ended on May 15, 2019. During this period, we included 25,890 patients with HTN. Data were collected by 321 investigators from 24 Tunisian districts. The investigators were doctors working in the private and public sectors. Cardiologists included 71% (n=18,382) of the patients, and general practitioners included approximately 25% (n=6473) of the patients.

Discussion

Study Significance

NATURE-HTN is the largest observational registry in the field of HTN management in Tunisia. The results will be compared to those of the TAHINA study. The latter was a national survey including 8007 patients aged between 35 and 70 years. The prevalence of hypertension was 30.6%, and it was higher in women (n=2682, 33.5%) than in men (n=2186, 27.3%). Only 38.8% (n=3107) of those with HTN were aware of their diagnosis, of which 84.8% (2635/3107) were receiving treatment. BP control was achieved in only 24.1% (635/2635) of the treated hypertensive patients. Women were more aware than men (1202/2682, 44.8% vs 630/2186, 28.8%), but the rates of treatment and control of HTN did not differ between the 2 genders. Higher age, being female, lower education level, and urban area emerged as important correlates of HTN awareness [15]. Certainly, there is an urgent need for comprehensive integrated population-based intervention programs to ameliorate the growing problem of HTN in Tunisians. BP control has not improved even in the developed countries. In France, according to the Flash studies, the percentage of the participants with BP is approximately 51%, and the use of monotherapy is one of the major problems registered in the French survey [17].

Conclusions

BP control should be continually evaluated through observational studies involving different populations to conduct intervention programs and reduce the burden of HTN in developing countries.

Data Availability

The data is the property of the Tunisian Society of Cardiology and cannot be distributed anywhere. The primary use of these data will be to describe the epidemiological profile of hypertension in Tunisia, determine the cardiovascular risk level of Tunisian hypertensive patients, and obtain an idea about the percentage of patients treated for therapeutic purposes. The planned secondary uses are to inform all physicians who may be involved in the management of Tunisian hypertensive patients (general practitioners, cardiologists, nephrologists, endocrinologists…) and to prepare a guide (in collaboration with the Ministry of Public Health), based on the outcomes of the registry, so that they can improve the level of hypertension control.

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
DBP: diastolic blood pressure
ESC: European Society of Cardiology
ESH: European Society of Hypertension
HTN: hypertension
LVH: left ventricle hypertrophy
NATURE-HTN: National Tunisian Registry of Hypertension
SBP: systolic blood pressure

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Protocol

A Family-Centered Sexual Health Intervention to Promote Cervical Cancer Screening Uptake Among Low-Income Rural Women in India: Protocol for a Community-Based Mixed Methods Pilot Study

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Abstract

Background: Human papillomavirus (HPV) is the primary cause of cervical cancer, which is preventable through screening and early treatment. The Papanicolaou (Pap) test and visual inspection with acetic acid (VIA), which are traditionally performed in clinical settings, have been used effectively to screen for cervical cancer and precancerous changes and reduce cervical cancer mortality in high-income countries for many decades. However, these screening methods are not easily accessible to women living in low- and middle-income countries, especially women living in rural areas.

Objective: The project will use HPV self-sampling, which will be supported by a sexual health literacy intervention, to increase rural women's participation in cervical cancer screening. The objectives are to determine the effectiveness of this program in (1) increasing sexual health literacy, (2) reducing the gendered stigma of HPV and cervical cancer, and (3) promoting cervical cancer screening by using HPV self-sampling.

Methods: The pilot study will use a community-based, family-centered, mixed methods design. We will recruit 120 women aged 30 to 69 years who are underscreened or were never screened for cervical cancer, along with 120 supportive male relatives or friends from 3 low-income rural/tribal villages in Maharashtra, India. Participants will attend gender-specific sexual health education sessions, followed by a movie matinee. Data will be collected through an interviewer-administered questionnaire before and after sexual health education sessions. The questionnaire will include items on social demographics, medical histories, attitudes, sexual health stigma, cervical cancer knowledge, and screening practices. Women will self-select whether to use HPV self-sampling. Those who do not may undergo a Pap test or VIA. Participants' views regarding barriers and facilitators and their suggestions for improving access and uptake will also be elicited. This protocol was approved by the research ethics boards of Toronto Metropolitan University (formerly known as Ryerson University; reference number: REB 2020-104) and Tata Memorial Center (reference number: OIEC/3786/2021 /00003).

Results: The Preventing Cervical Cancer in India Through Self-Sampling study was funded in January 2020 for 15 months. Due to the COVID-19 pandemic, the project was extended by 1 year. The study outcome measures will include changes in knowledge and attitudes about cervical cancer screening, the proportion of participants who self-select into each cohort, the proportion of positive test results in each cohort, and the proportion of participants with confirmed cervical cancer. Women's experiences regarding barriers and facilitators of screening uptake will be captured.

Conclusions: Our multifaceted work could lead to reduced cervical cancer mortality and morbidity and increased community capacity in sexual health promotion and cervical cancer prevention. The insights and lessons learned from our project can be used

to inform the adaptation and scale-up of HPV self-sampling among women across India and in other countries; promote collective commitment to family-centered wellness; and support women to make healthful, personalized cervical screening decisions.

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cervical cancer screening; human papillomavirus self-sampling; India; low income; sexual health; health literacy; women; family-centered care; rural area; rural; sexual health literacy; human papillomavirus; screening; cancer screening; cervical; cancer; sexually transmitted infection

Introduction

Cervical cancer is a vivid indicator of global health disparity, as 90% of all deaths due to cervical cancer occur in low- and middle-income countries [1]. It is one of the leading causes of cancer-related mortality worldwide, and India accounts for 16% of cervical cancer cases and 30% of cervical cancer deaths globally [1-4]. Every year in India, 96,922 new cervical cancer cases are diagnosed, and 60,078 women die due to late diagnosis and no access to lifesaving treatment [2,4]. It is the second leading cause of cancer death in women aged 15 to 44 years in India [2]. Virtually all cases of cervical cancer are caused by human papillomavirus (HPV), which is transmitted primarily through sexual intercourse. Cervical cancer has profound negative impacts on individual life expectancy, the quality of family life, and personal and societal economic burden. However, premature death due to cervical cancer and disability resulting from cervical cancer are preventable tragedies that can be avoided through regular screening. With appropriate screening, cervical cancer is highly preventable. In many high-income nations, the incidence and mortality of cervical cancer have declined steadily and steeply as a result of the widespread use of the Papanicolaou (Pap) test as a screening tool. However, the coverage of cervical cancer screening is 19% in low- and middle-income countries and 63% in high-income countries [5]. Moreover, preadolescent HPV vaccination is too expensive for widespread use in low-income countries, given its social, logistical, and financial challenges.

Cervical cancer screening and testing for the HPV viruses are available at urban private medical centers in India but not in government health centers. The burden of preventing cervical cancer is solely carried by the Indian women themselves, with little support or resources. Women in rural India are particularly vulnerable because they often have no knowledge about screening or have no access to screening services, and many have low literacy and no access to education and resources, including financial resources [6]. Furthermore, many of them get married at ages as young as 15 years, even though the legal age of marriage in India is 18 years [7], meaning that they become sexually active at a young age. They are also often socially and economically dependent on the men in their families [8], are often excluded from decision-making, and are often restricted in terms of mobility [9]. Studies that have been conducted with women in India and among the South Asian diaspora in high-income countries have found limited knowledge about cervical cancer and the benefits of screening among the participants [10,11]. Furthermore, misconceptions and stigmas surrounding sexually transmitted infections (STIs), including HPV, may deter the uptake of screening due to the entrenched gender norms and stereotypes associated with infections (eg, women with STIs may be viewed as immoral or corrupt, among other demeaning labels). Engaging both men and women in cervical cancer screening and normalizing, destigmatizing, and talking openly about cervical cancer and screening are important steps in reducing cervical cancer mortality and morbidity. Male partners' involvement in sexual and preventive health care has been shown to not only be an effective strategy in women's health outcomes but also be acceptable to women in general [12-16]. The World Health Organization recommends men's engagement in the prevention of cervical cancer in low- and middle-income countries [16]. Men play a significant role in their female partners' access to health services, as they are the main source of financial support for costs related to transportation and health services. Moreover, they hold the primary power in granting permission for using these health services. Thus, it is imperative to provide alternative, accessible, acceptable, innovative, and family-centered screening strategies that could help reduce observed cervical cancer disparities.

HPV self-sampling is an easy and user-friendly method that has been shown to be highly acceptable among women in diverse racial, ethnic, religious, and age groups in many countries [17-31]. This alternative approach has been found to be effective in engaging underscreened and never-screened (UNS) women to increase their participation in cervical cancer screening and reduce related mortality and morbidity, thereby improving the overall quality of life among women [18,19,21,22,25,27,28]. It does not require a health care provider to either perform a pelvic examination (whereas Pap tests do require a health care provider) or conduct a vaginal speculum examination that involves applying diluted acetic acid (vinegar) to the cervix. This means that there is no need for traveling to medical centers, which often is a barrier. HPV self-sampling provides an opportunity for empowering women by allowing them to conduct such tests in the privacy of their own homes and at a time that is convenient to them. Offering this approach as a screening alternative for UNS groups could lead to increased participation and a resultant reduction in cancer screening inequalities.

This paper presents the study protocol for an international study titled *Preventing Cervical Cancer in India Through Self-Sampling (PCCIS)*. This is a family-centered, community-based, mixed methods pilot project that aims to improve the health of rural Indian women residing in the state of Maharashtra through capacity building and by reducing

avoidable health disparities that are associated with HPV and cervical cancer. A key focus of this project is to promote gender equity through collective empowerment and capacity building. Gender equity is achieved through increasing women's access to lifesaving tests and health resources, enabling equitable decision-making, and changing attitudes by engaging both men and women as families. This family-centered approach will contribute to open dialogues about and solutions for reducing stigma and improving community health literacy with regard to HPV and cervical cancer screening and, consequently, will increase cervical cancer screening uptake.

Methods

Study Design

We will use a community-based mixed methods design to assess the effectiveness of a family- centered program that involves using HPV self-sampling, which will be supported by a sexual health literacy intervention, to increase rural women's participation in HPV and cervical cancer screening. The study objectives are to determine the effectiveness of this program in (1) increasing sexual health literacy, (2) reducing the gendered stigma of HPV and cervical cancer, and (3) promoting cervical cancer screening by using HPV self-sampling.

Target Population

We will engage 3 rural/tribal villages—Shirgoan in Phalghar district, Khodala in Mokhada district, and Jamsar in Jawhar district—in the state of Maharashtra, which is the second most populated state of India; Maharashtra has a population of over 128 million people and a high prevalence of advanced cervical cancer. Approximately 55% of Phalghar's total population lives in rural areas. The literacy rate in Phalghar is about 67% (59% for women and 72% for men). However, the literacy rate drops significantly in the rural areas of this district. For example, the literacy level is reported to be 46% in Mokhada and 48% in Jawhar. The women in these areas are expected to have all of the risk factors pertaining to cervical cancer and reproductive tract infections. The primary health center has no organized cervical cancer screening program. The women in these villages need to travel about 50 km to access medical facilities [32,33].

Participants and Recruitment Strategies

The women in the above-mentioned villages are the primary target population of our project, and supportive men in their families (eg, fathers, brothers, spouses, cousins, and sons) are the secondary target population. We will recruit 120 women and 120 men from the women's families.

Our project will build capacity by training trusted female community members in these villages to act as community champions and help recruit and educate women about cervical cancer and the use of HPV self-sampling. The community champions will be *localaccredited social health activists* (termed *ASHA*, meaning *hope*)—a new model of care that was adopted by the Indian government; it relies on building capacity in local and remote areas by recruiting trusted community members and training them to promote awareness about the health-related issues facing their respective communities. The community champions will assist with the participants' recruitment. Once the women agree to participate, they will be invited to identify a "supportive" man in their life (eg, a spouse, father, brother, cousin, or son) whom they feel can play a positive and influential role in health promotion within their villages.

The eligibility criteria for female participants include (1) UNS women (ie, a self-report of >4 years since their last Pap test or visual inspection with acetic acid [VIA], including no history of a Pap test or VIA); (2) women aged 30 to 69 years old; (3) women residing in Shirgoan, Khodala, and Jamsar in the state of Maharashtra, India; (4) women who have ever been sexually active; (5) women who are able to provide informed consent; and (6) women who are willing to share contact information with the study team. The exclusion criteria include (1) being pregnant and (2) having a history of hysterectomy or past treatment for precancerous or cancerous cervical lesions.

Male participants' eligibility criteria include (1) being a male family member (husbands, fathers, brothers, sons, and cousins) of the UNS female participants, (2) being identified and referred by UNS female participants, and (3) being aged 18 years or older.

Theoretical Framework

Our study will be guided by the Population Health Promotion framework [34] (Figure 1), which is grounded in the principles of social justice and equity and uses a socioenvironmental approach to address health disparities [35,36]. This research approach is aligned with the 2018 Whistler Principles to Accelerate Innovation for Development Impact [37]. Our research approach recognizes that individual and collective health are intertwined and that health disparities are the outcomes of intersecting social determinants, including access to economic and social resources, everyday encounters of gender-based discrimination, and social exclusion [38,39]. It is underpinned by the concepts of (1) community empowerment, a process that promotes the participation of people, organizations, and communities toward the goal of increased individual and community control, the improved quality of community life, and social justice, and (2) capacity building, in which existing human and social resources are leveraged to solve collective problems and improve the well-being of a community's members through informal and formal social processes and organized efforts [35,38].

We will also use the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [40,41] (Figure 2) to evaluate the overall public health impact of our intervention. This framework allows for the comprehensive assessment of public health programs in a real-world setting. We will assess whether we are *reaching* our intended target of UNS rural Indian women and the supportive men in their lives; whether the intervention is *effective* by quantifying screening uptake, normal and abnormal screening test results, and their end results; how many women and providers *adopt* the intervention over the study period; how much training, education, and staff time are required in *implementation*; and whether the screening program is *maintained* after the study period.

Figure 1. Population Health Promotion Model [34].

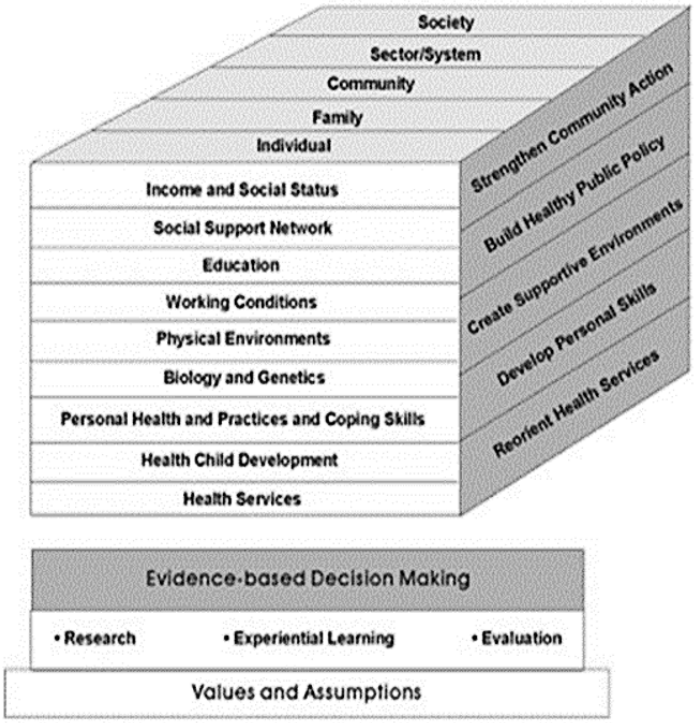

Figure 2. The RE-AIM framework. RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

Study Intervention

The project is a community-based, action-oriented intervention with the following two components: education and access to cervical cancer screening. The central hypotheses that we will address are that (1) there will be an increase in sexual health literacy (knowledge) and a reduction in sexual health stigma (attitudes) related to cervical cancer and screening after participating in the study and (2) there will be a higher uptake of HPV self-sampling compared to that of traditional methods of screening (VIA and Pap test) among UNS women. To test these two hypotheses, we will begin with the education component, which will be followed by inviting women to take part in HPV self-sampling.

Education to Promote Sexual Health and HPV Screening

The sexual health literacy intervention is family- and community-centered. The intervention activities will promote the awareness and sexual health literacy of both men and women in our three targeted villages. Strong evidence indicates that family- and community-centered approaches are needed to

advance gender equity because (1) women and girls do not live and are not socialized in a vacuum, (2) decisions about every aspect of the lives of women and girls are embedded in their family relationships and intimate relationships, and (3) the stigma of HPV and cervical cancer is often reinforced by dominant society norms and misconceptions [42]. By investing in a program that increases sexual health knowledge among women, the men in their families, and their communities as a whole, we anticipate that the program's impact will be sustainable.

Since the literacy level of the women and men in the three selected villages is low, we will use a storytelling health communication approach that has been proven to be effective in promoting adult health literacy [43,44]. Storytelling is an integral aspect of everyday life. Stories enable participants to engage with the content in ways that allow them to make sense of the content in the context of their own lives, such as through self-reflection and dialogue with others [45,46]. Furthermore, stories are effective in reducing stigma [38] and changing attitudes, as they carry the power to engage the audience emotively to promote empathy, shape perspectives, and motivate action [47,48]. Storytelling is a well-established and well-accepted means of cultural learning and empowerment in India [49,50]. It is also a strategy for sharing knowledge, particularly among women who have been historically left out of more formal learning institutions [51].

To ensure that the project activities are socially relevant and culturally appropriate, we will establish a project advisory committee (PAC) prior to implementing the project. The PAC will be made up of local community members (including both men and women), women advocates, service providers, decision makers, and relevant stakeholders. We will actively engage the PAC in all stages of the project to provide support for design refinement, community engagement, recruitment, the interpretation of results, and knowledge translation and exchange activities. With input from the PAC, we will develop culturally appropriate education materials and videos in Hindi and Marathi—the predominant languages spoken in Maharashtra. Storytelling will be used in the following three accessible formats to promote learning: graphic novels, short videos, and testimonials from service providers and health professionals. In addition, infographics and illustrations will be used to support women in learning how to perform HPV self-sampling, along with support from the community champions and health professionals. Together, these materials will promote knowledge about the HPV virus, cervical cancer, cervical screening, HPV self-sampling, sexual health, and general health as family resources.

Gender-Specific Sexual Health Education Sessions

We will hold 24 gender-specific sexual health education (SHE) sessions—12 for women and 12 for men. A male clinician will lead the men's sessions, and a female clinician will lead the women's sessions. Each information session will be approximately 90 to 120 minutes in length and consist of 10 participants. The topics will include the HPV virus in the context of STIs, the stigma surrounding cervical cancer, the method of HPV virus transmission, the male and female cancers that result from HPV infection, the risk factors of cervical cancer, and the importance of screening. Questions about knowledge, attitudes, and stigma will be adopted from validated questionnaires and will be reviewed by the PAC for cultural relevance and appropriateness. Other gender-specific content, which will be identified through consultations with the PAC and local team members, will be included to facilitate increased health literacy and promote participants' interest.

All participants will then be invited to attend a movie matinee on the same day as the SHE. The contents of the video for the movie matinee will be drawn from clinical cases and will include stories of two women—one who died of cervical cancer (ie, a movie about how her death impacted her spouse and family) and another who was screened, was diagnosed, received treatment, and recovered. This video will be followed by short testimonial videos from health care professionals, those from affected women and family members, and a period in which the audience can ask questions and receive answers. Packed food and refreshments will be served at these sessions. The SHE sessions and the movie matinee will be held in a venue, and in accordance with the local COVID-19 guidelines, we will ensure proper social distancing and the wearing of masks and personal protective equipment by all attendees. All participants will complete an interviewer-administered questionnaire before and after the SHE sessions. At the end of the movie matinee, all participants will be surveyed on their intention to take part in HPV self-sampling. They will be given 3 colored paper ribbons with preprinted potential participation codes when they arrive (red=no; green=yes; orange=undecided), which will represent their family-centered decision to participate in HPV self-sampling. In other words, the decision to undertake screening will be made together by female participants and their selected male participants at the end of the movie matinee, so that only 1 color-coded ribbon will be selected by each couple and shared with the research staff.

HPV Testing Process and Benchmarks

Based on the responses that we receive at the end of the movie matinee, female participants will be divided into 2 self-selected cohorts. Cohort A will consist of eligible women who are willing to use the HPV self-sampling kit. Cohort B will consist of eligible women who do not agree to use the kit but consent to participate in the study, and they may or may not undergo VIA or a Pap test.

Our Indian study collaborators and informants indicated that we should expect to recruit ≥100 women in cohort A and 20 in cohort B over the study period. Those who are interested in trying HPV self-sampling will be provided with a kit that they can take home and a visual instruction pamphlet that displays how to collect a sample. They will be told that a female health professional will pick up their self-collected specimen within 48 hours. The female health professional will then collect the specimens and take them to the designated hospital labs. Those who test negative for HPV will be informed by their respective female health professional, and their names will be included in a database that will be developed and maintained by our local partners, so that these participants can be contacted again for screening in 5 years. Those who test positive will undergo VIA

or a Pap test in a designated community place. The tests will be performed by either our research health care providers or local gynecologists, who will be trained by our Indian study collaborators.

Medical follow-up tests and treatments will be arranged by our Indian study collaborators for participants with positive Pap test results. For women in cohort B who refuse HPV self-sampling but agree to undergo VIA or a Pap test, our medically trained female health professional will either perform VIAs or arrange their Pap tests through our medical collaborators. Those with negative VIA test or Pap test results will be informed by our health professional, and their names will be added to the database, so that they can be contacted in 3 years. Those with positive Pap test results will undergo follow-up tests and treatments, as described above.

Key Outcome Indicators

Informed by the Population Health Promotion and the RE-AIM frameworks, we will monitor and measure the following key indicators:

- Screening outcomes (among those who participate): the number of women screened (through self-sampling vs through VIA or a Pap test), the number of HPV-positive women detected by each screening method, the number of HPV-positive women that followed up by undergoing a Pap test, and the number of Pap-tested women referred to colposcopy (follow-up)
- Acceptability and preference outcomes: the usability of the screening kit and instructions, confidence in the sample collected, comfort with and preference for self-sampling versus VIA and Pap test, and preferences for screening locations (home, clinic, or other)
- Education outcomes: changes in sexual health literacy (knowledge) about cervical cancer risk factors and screening (overall and by gender) and changes in attitudes (gendered stigma) toward cervical cancer risk factors and screening (overall and by gender)
- Cost-benefit analysis: net present value methodology will be used, which involves estimating the difference between the total discounted benefits and the total discounted costs for each of the cervical screening modalities (ie, HPV self-sampling vs VIA and Pap test)

Mixed Methods of Data Collection

Informed consent will be obtained prior to data collection. Data will be gathered by using both quantitative and qualitative tools, which include interviewer-administered questionnaires, interviews, and focus groups.

Before and After SHE Sessions

All female and male participants will complete an interviewer-administered questionnaire before and after the SHE sessions. The questionnaire will include items on social demographics, medical histories, the stigmas surrounding and attitudes toward cervical cancer and screening, cervical cancer knowledge, screening practices, and relevant gender-specific questions (eg, those about menstruation and pregnancies). In addition, the women will be asked whether they would undergo cervical cancer screening and, if so, which of the methods of screening (VIA and Pap test or self-sampling) would they undergo and why. The men will be asked similar questions about whether they would encourage their female loved ones (mothers, sisters, cousins, or daughters) and about their preferred method of screening. Notes will be taken during the question and answer period in the SHE sessions to aid our understanding of participants' knowledge, attitudes, and perspectives.

Cervical Cancer Screening Uptake and Results

Data will be collected about the number of women screened (through self-sampling vs through VIA or a Pap test), the number of HPV-positive women detected by each screening method, the number of HPV-positive women that followed up by undergoing a Pap test, and the number of Pap-tested women referred to colposcopy (follow-up).

Focus Group Consultations

We will engage women in 6 focus groups—4 with women from cohort A and 2 with women from cohort B. We will compile a list of female participants who express an interest in being contacted for the focus groups. We will then randomly select and invite women from each cohort until we recruit 8 to 10 women per focus group. Focus groups with women from cohort A will explore their experiences with, barriers to, and facilitators of using HPV self-sampling and suggestions for improving access and uptake. Further, 1 of the 4 focus groups will be for women with positive HPV results and will explore their care trajectory. Focus groups with women from cohort B will explore barriers and facilitators to the use of the kit and attitudes toward screening. One-on-one interviews will be arranged for women who have concerns about participating in focus groups. In addition, we will hold 2 focus groups (8-10 participants per focus group) with male participants to elicit their views about the project intervention and explore their perceived barriers and facilitators to the undertaking of cervical cancer screening by their female family members. These two focus groups will be held with health care providers to ascertain male participants' views about HPV self-sampling and recommendations for practice and policy. All focus groups will last for approximately 90 minutes; will be facilitated by at least 2 members of the research team; and will be audio-recorded, transcribed, and translated to English by trained bilingual team members.

Data Analysis Planning

Quantitative data analyses will be conducted by using SPSS 26 (IBM Corporation). Univariate descriptive statistics will be used to profile the study participants based on their survey responses. Inferential statistics, including dependent and independent 2-tailed *t* tests, 1-way ANOVA tests, and chi-square tests, will be performed to assess mean score differences for each outcome measure (eg, cervical knowledge, attitudes, and STI stigma) across and within study cohorts. Furthermore, bivariate and multivariate analyses, if feasible based on the sample size, will be conducted to determine the variables associated with HPV self-sampling uptake and predictors of screening practices.

Audio-recorded focus group interviews will be transcribed verbatim in Hindi and Marathi and translated into English. Each translated transcript will be reviewed and verified by at least 2

bilingual research team members to ensure cultural equivalence. A computer software program (NVivo; QSR International) will be used to aid with data management. For the data analysis, both inductive and deductive analyses will be applied to manually look for broad categories that are indigenous (articulated by the participants) and sensitizing (drawn from pre-existing theories and concepts) in the transcripts [52]. We will begin with the development of a coding framework that is informed by participants' narratives, the research questions, and the RE-AIM framework. We will use a systematic approach that involves (1) familiarizing ourselves with the data; (2) generating initial codes; (3) developing a coding tree to guide the coding of transcripts; (4) identifying themes; (5) reviewing, defining, and naming themes; (6) analyzing and interpreting the narratives; and (7) producing reports and relevant documents based on the results. In addition, we will apply the triangulation of methods approach to a systematic comparison to verify study findings, elucidate complementary aspects of phenomena, and examine points of convergence and divergence for data that are specific to the different processes and outcomes of implementation.

Ethics Approval

The study protocol received full ethical approval from the research ethics boards of Toronto Metropolitan University (formerly known as Ryerson University; reference number: REB 2020-104) and Tata Memorial Center (reference number: OIEC/3786/2021 /00003) in June 2021 and August 2021, respectively.

Results

The anticipated short-term outcomes of our project are (1) increased HPV self-sampling among UNS women; (2) increased awareness and knowledge of HPV and cervical cancer among women and the men in their families; (3) increased sexual health literacy and knowledge among women and men in the three villages; (4) increased capacity among local community health professionals, health workers, and graduate students to carry out similar initiatives; (5) evidence of changes in gender norms to support gender and health equity; and (6) new available evidence for informing local and regional public health policies about how to advance HPV and cervical cancer screening in rural India.

The Preventing Cervical Cancer in India Through Self-Sampling study was funded in January 2020 for 15 months. Due to the COVID-19 pandemic, the project was extended by 1 year.

Discussion

The anticipated main findings of our project are an increase in women's uptake of cervical cancer screening and a higher propensity for using HPV-self sampling, which would corroborate earlier research on the feasibility and acceptability of self-sampling among low-income and marginalized women [17-31]. The project will also promote awareness, sexual health literacy, and the reduction of stigma among the studied communities by targeting both men and women. The engagement, partnership, and support of the male population in these communities will be critical in promoting women's sustained uptake of cancer screening. The project will build capacity within low-income villages in India by training female community members and female health workers to educate women about cervical cancer and the use of HPV self-sampling. All of the sexual health educational resources that will be developed for this study, which will include storyboards, infographics, and videos, can be used with other communities across India that face this health challenge. Furthermore, our local collaborators have established strong connections with local government health agencies. Early on in the project, our local project coordinators will communicate with local government health agencies, which were identified by our local partners, and keep them informed about the study and its progress. The findings will be presented to local government agencies by our local partners. The proposed project, with its focus on women's health, could result in the implementation of a high-value cervical screening program in other countries and contexts.

The evidence gained from the implementation of HPV self-sampling, the promotion of sexual health literacy, and the cost-benefit analysis will be used to advance public health policies and inform the scale-up of similar initiatives in other villages and states across rural India. Our project has the potential to impact thousands of women in India and other low-income countries.

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Authors' Contributions

MV—the nominated principal investigator—contributed to the initial draft of the manuscript, while JPHW, AKL, GM, and SP—the coprincipal investigators—reviewed, revised, and endorsed the final submission.

Conflicts of Interest

None declared.

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Abbreviations

HPV: human papillomavirus
PAC: project advisory committee
Pap: Papanicolaou
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SHE: sexual health education
STI: sexually transmitted infection
UNS: underscreened and never-screened
VIA: visual inspection with acetic acid

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Protocol

A Patient Decision Aid (i.ARTs) to Facilitate Women's Choice Between Oral and Long-Acting Injectable Antiretroviral Treatment for HIV: Protocols for its Development and Randomized Controlled Pilot Trial

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Abstract

Background: Many women with HIV (WWH) have suboptimal adherence to oral antiretroviral therapy (ART) due to multilevel barriers to HIV care access and retention. A long-acting injectable (LAI) version of ART was approved by the US Food and Drug Administration in January 2021 and has the potential to overcome many of these barriers by eliminating the need for daily pill taking. However, it may not be optimal for all WWH. It is critical to develop tools that facilitate patient-provider shared decision making about oral versus LAI ART modalities to promote women's adherence and long-term HIV outcomes.

Objective: This study will develop and pilot test a web-based patient decision aid called i.ART+support (i.ARTs). This decision aid aims to support shared decision making between WWH and their providers, and help women choose between oral and LAI HIV treatment.

Methods: The study will occur in 3 phases. In phase 1, we will utilize a mixed methods approach to collect data from WWH and medical and social service providers to inform *i.ARTs* content. During phase 2, we will conduct focus groups with WWH and providers to refine *i.ARTs* content and develop the web-based decision aid. In phase 3, *i.ARTs* will be tested in a randomized

controlled trial with 180 women in Miami, Florida, and assessed for feasibility, usability, and acceptability, as well as to evaluate the associations between receiving i.ARTs and viral suppression, ART pharmacy refills, and clinic attendance.

Results: This study was funded in March 2021. Columbia University's IRB approved the study protocols (approval number IRB-AAAT5314). Protocols for phase 1 interviews have been developed and interviews with service providers started in September 2021. We will apply for Clinicaltrials.gov registration prior to phase 3, which is when our first participant will be enrolled in the randomized controlled trial. This is anticipated to occur in April 2023.

Conclusions: This study is the first to develop a web-based patient decision aid to support WWH choices between oral and LAI ART. Its strengths include the incorporation of both patient and provider perspectives, a mixed methods design, and implementation in a real-world clinical setting.

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KEYWORDS

patient decision aid; HIV treatment; oral ART; long-acting injectable ART; study protocol; women's health

Introduction

Suboptimal antiretroviral therapy (ART) adherence among people with HIV has constrained efforts to curb the HIV epidemic in the United States [1]. Women face myriad barriers to HIV care and treatment and have historically been underrepresented in clinical trials for HIV treatment [2,3]. As a result, women with HIV (WWH) have lower care retention (58% retention versus 65% retention in the overall US population), which contributes to their increased mortality compared with men [1,4-7]. There is therefore an urgent need for strategies that optimize care engagement and viral suppression among WWH.

Long-acting injectable (LAI) ART may be a strategy to improve ART adherence and HIV outcomes for women [2,3,8]. The first LAI ART (cabotegravir/rilpivirine), which consists of monthly intramuscular injections rather than daily pills, was approved by the US Food and Drug Administration (FDA) in January 2021; a bimonthly version was approved in February 2022; and other LAI ART drugs are in advanced stages of clinical trials and expected to be available for HIV treatment in the near future [9]. Women comprised only 8%-33% of phase 2 and phase 3 LAI ART trial participants, and pregnant women were not included [10-13]. As such, gender-specific barriers, pregnancy-related interactions [13] and characteristics that promote ART adherence among WWH remain underexplored [14-16]. Furthermore, LAI ART research has occurred largely among clinical trial participants, whose optimal medication adherence and clinic attendance do not represent the majority of WWH [17].

While preliminary research suggests that most WWH would prefer LAI ART over their current daily oral medication [18], this research has also identified multilevel barriers to LAI ART uptake. At the *individual level*, these include women's concerns about side effects, pregnancy-related interactions, and drug resistance if LAI ART is discontinued without oral ART initiation; at the *clinic level*, barriers include medical mistrust due to historic sterilization campaigns [19] and lack of provider knowledge and willingness to offer LAI ART; and at the *structural level*, barriers include gender-specific socioeconomic inequalities and dynamics such as low-wage employment with unstable scheduling, lack of transportation, and care-taking responsibilities. Furthermore, FDA indication still requires viral suppression via oral ART prior to initiating LAI. These multilevel barriers could all complicate the frequent visits that LAI ART administration will require [18,20-23]. WWH and providers may benefit from tools and strategies that help them to identify and address barriers that prevent uptake of, and adherence to, LAI ART.

Shared decision making in medical settings is often accomplished using patient decision aids. These evidence-based tools promote equity in medicine by increasing patients' knowledge, decision-making power [24,25], and health outcomes [26-28]. This approach can also lower medical paternalism [24,29-31]. Patient decision aids can improve medication adherence directly [32], as well as through mediating factors (eg, patient satisfaction [33-35], efficacy [36-38], and communication) [33,39,40]. These tools are ideal for preference-sensitive decisions with multiple options [41,42]; however, no patient decision aids yet exist to facilitate women's choice between HIV treatment modalities. New tools are urgently needed to ensure the successful and equitable integration of new technologies such as LAI ART into clinical settings [43].

This paper describes the protocol for a mixed methods study to develop, refine, and test a patient decision aid for WWH, called i.ART+support (*i.ARTs*). *i.ARTs* will facilitate shared decision making between WWH and providers to determine which HIV treatment (oral or LAI ART) best fits a woman's preferences, addresses her unique barriers, and, in doing so, facilitates adherence. This study will be conducted within the MACS/WIHS Combined Cohort Study (MWCCS) [44] and will fill the aforementioned gaps in existing research regarding patient decision aids for WWH. MWCCS is the largest and oldest prospective epidemiological cohort study of HIV in the United States. The current cohort includes approximately 1800 women from geographically diverse sites across the United States. Each of these has associated clinical sites with medical and social service providers who work with WWH. The aim of this paper is to provide an overview of all procedures for our study focused on developing a patient decision aid to support

WWH as they choose between LAI and oral formulations of ART.

Methods

Overview of the Study

Study methods are aligned with current systematic approaches to patient decision aid development [36,45,46], and will occur in 3 phases (Figure 1). Each phase is associated with 1 of the following study aims. *Phase 1* will generate data to inform *i.ARTs* content using mixed methods research with WWH and providers. *Phase 2* will iteratively develop *i.ARTs* as a web-based patient decision aid. *Phase 3* will pilot test *i.ARTs* to assess feasibility, acceptability, and usability and to compare decisional outcomes and adherence data (including viral suppression, ART refills, and clinic attendance) between *i.ARTs* recipients and standard of care (control) WWH (n=180; 90 per group). Each phase includes distinct data collection activities, which are summarized in Table 1.

Figure 1. Study overview. *i.ARTs*: i.ART+support; LAI ART: long-acting injectable ART; MWCCS: MACS/WIHS Combined Cohort Study; WWH: women with HIV.

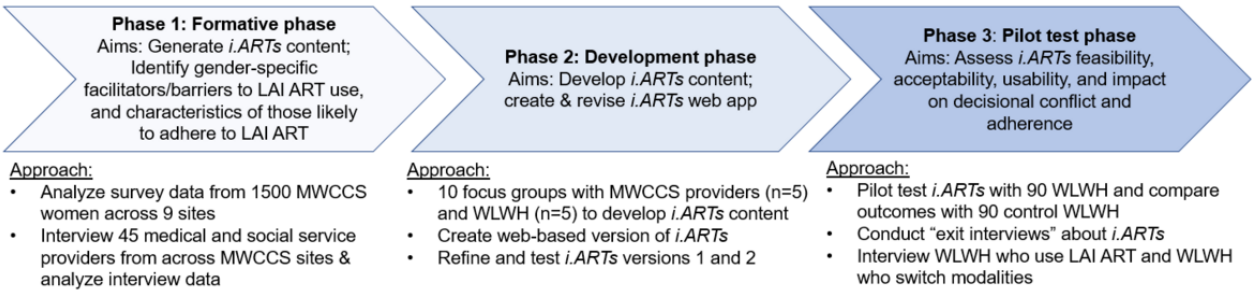


Table 1. Overview of data sources and participants.

Phase	Data source	Participants	Scope of data	Purpose
1	MWCCS[a] 2020 cohort survey	1500 WWH[b] at 9 MWCCS sites	WWH perspectives on LAI ART[c] and decision making; identify relevant barriers and facilitators to LAI ART uptake; characteristics of women who are most likely to adhere to LAI ART	Generate *i.ARTs*[d] content
1	Provider interviews	45 medical/social service providers at MWCCS sites	Provider perspective on characteristics of women most likely to adhere to LAI ART; reasons providers would not offer LAI ART to a woman for whom it is clinically indicated; provider perceptions of multilevel barriers and facilitators to WWH's ART use	Generate *i.ARTs* content
2	Focus groups	MWCCS providers, WWH in Miami, Florida	Feedback on successive iterations of *i.ARTs*	Develop and refine *i.ARTs* content
3	Baseline and postvisit survey	180 WWH (90 from the intervention/*i.ARTs* arm and 90 from the control arm)	Information on decisional conflict (baseline and post), acceptability and satisfaction (post only), and sociodemographic and behavioral moderators (baseline only)	Assess *i.ARTs* acceptability and usability outcomes, assess impact of moderators
3	Exit interviews	20 WWH who receive *i.ARTs* and 10 providers	WWH and provider perspectives on *i.ARTs* tool	Assess *i.ARTs* feasibility, usability, acceptability
3	Electronic medical record data	180 WWH	*i.ARTs* adherence data for study participants, including clinic visits, medication refills, and viral load data	Preliminary impact of *i.ARTs* data on treatment-related outcomes

[a]MWCCS: MACS/WIHS Combined Cohort Study.

[b]WWH: women with HIV.

[c]LAI ART: long-acting injectable antiretroviral therapy.

[d]*i.ARTs*: i.ART+support

Phase 1: Formative Work to Inform *i.ARTs* Content

To ensure *i.ARTs* addresses a comprehensive array of factors that influence LAI ART uptake, phase 1 includes data collection that incorporates the perspectives of both WWH and providers at MWCCS sites.

Phase 1a will quantitatively assess WWH perspectives on LAI ART and decision making, identify relevant barriers and facilitators to LAI ART uptake, and identify the characteristics of women who are most likely to adhere to LAI ART. It utilizes survey data administered to the MWCCS study cohort starting in October 2020. Historically, this sample included 1661 WWH

of whom 1610 have a history of taking oral ART [44]. None have participated in LAI ART clinical trials. Full descriptions of participant recruitment, selection, enrollment, and study procedures for MWCCS are available elsewhere [44]. Survey responses from the 2020 cohort were collected from fall 2020 through summer 2021, and include 15 items that assess LAI ART–related knowledge, interest, and potential barriers and facilitators to use. We will use multivariable logistic regression models to identify factors associated with WWH's interest in, and barriers and facilitators to, LAI ART. While potential barriers and facilitators to LAI ART uptake can change over time (eg, transportation/housing), we will be looking at these associations cross sectionally and thus capturing these barriers at a given moment in time. The sample size provides the power to detect modest effect sizes in a multivariable logistic regression analysis (odds ratios ranging from 1.4 to 1.6), even with a low probability of LAI interest and a high squared multiple correlation (0.4-0.5) between predictor variables. This sample size will allow for subgroup analyses and still detect moderate effect sizes (eg, by age or MWCCS site).

Phase 1b assesses HIV provider perspectives on LAI ART for their female clients. It involves in-depth interviews with 30 medical (eg, infectious disease physicians, advanced practice registered nurses) and 15 social service providers (eg, case managers, HIV clinical social workers) who serve WWH across 9 MWCCS sites and affiliated clinical sites.

Provider participants will complete a 1-time, 45-60-minute interview, and receive a US $75 gift card as compensation. Interview domains will include (1) providers' perceived characteristics of women most likely to adhere to LAI ART, particularly compared with oral ART (eg, housing, oral ART adherence, caregiving responsibilities, and clinic attendance); (2) reasons providers would not offer LAI ART to a woman for whom it is clinically indicated; (3) providers' perspectives on decision making in the clinical setting and their experience in deciding which ART medications their WWH clients should take; and (4) multilevel barriers and facilitators to WWH's ART use and solutions to overcome these adherence barriers. These domains are determined by formative work by the study team [18,20,22,23]. Interviews will be digitally recorded and professionally transcribed. Transcripts will be coded using a set of codes inductively identified from the data; these will be supplemented by codes derived from the existing literature. A thematic content analysis approach will be used to identify key findings within domains of interest [47]. Data will be summarized and applied to activities in phase 2, described in the following section.

Phase 2: *i.ARTs* Development

Phase 2 utilizes sequential focus groups with both WWH and medical and social service providers to determine the content of *i.ARTs* and create and revise the *i.ARTs* web-based app. Existing research indicates that web-based decision aid tools have advantages over paper-based ones, including interactive interfaces and visual filtering and sorting options [48]. This stage of *i.ARTs* development will follow International Patient Decision Aids Standards Collaboration (IPDAS) guidelines [46,49,50] and use the Ottawa Decision Support Framework [27,51-53]. This framework explains the relationship between participants' decisional needs and decisional quality using both prescriptive [54] (based on rational actions, highest expected utility) and descriptive [55] (preferences-based, nonrational) decision theories.

An overview of the planned *i.ARTs* development process is included in Figure 2. We will conduct 2 sets of 5 focus groups: 1 set with 10 MWCCS providers recruited from the Phase 1 interview participants and the other set with 8-10 WWH recruited from the Miami MWCCS–affiliated clinical site. The Miami MWCCS site was selected due to the city's high HIV incidence and low ART adherence, as well as a racially/ethnically diverse population [56-58]. WWH will be selected from Miami's MWCCS community advisory board as well as by local MWCCS collaborators to ensure inclusion of women with a diverse range of perspectives, clinic attendance, and adherence. Each focus group will meet for approximately 60 minutes, and participants will be compensated US $40 per session for their time. We will record and transcribe the focus groups and review them to identify which items and topics should be included in the patient decision aid, as well as how to word specific items.

Focus groups will use data from phase 1 to develop and finalize *i.ARTs* content and iteratively refine the web-based version of *i.ARTs* to prepare for the phase 3 pilot testing according to the schedule in Figure 3. Between each set of focus group meetings, the study team will integrate feedback from both the provider and WWH groups and either create the suggested content or make the suggested improvements to the *i.ARTs* program. This will ensure that women's perspectives and realities will be captured to tailor the content within the patient decision aid.

Figure 2. *i.ARTs* decision aid development process and focus groups (FGs). *i.ARTs*: i.ART+support.

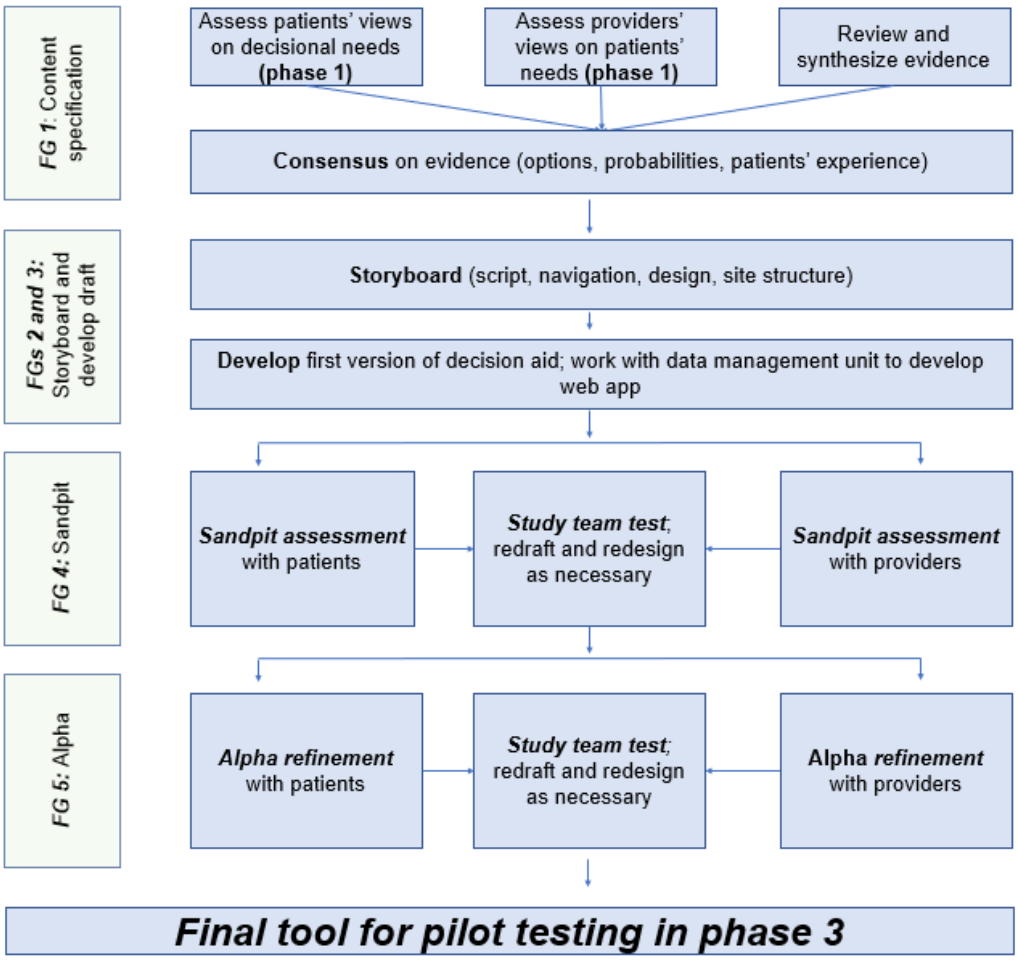
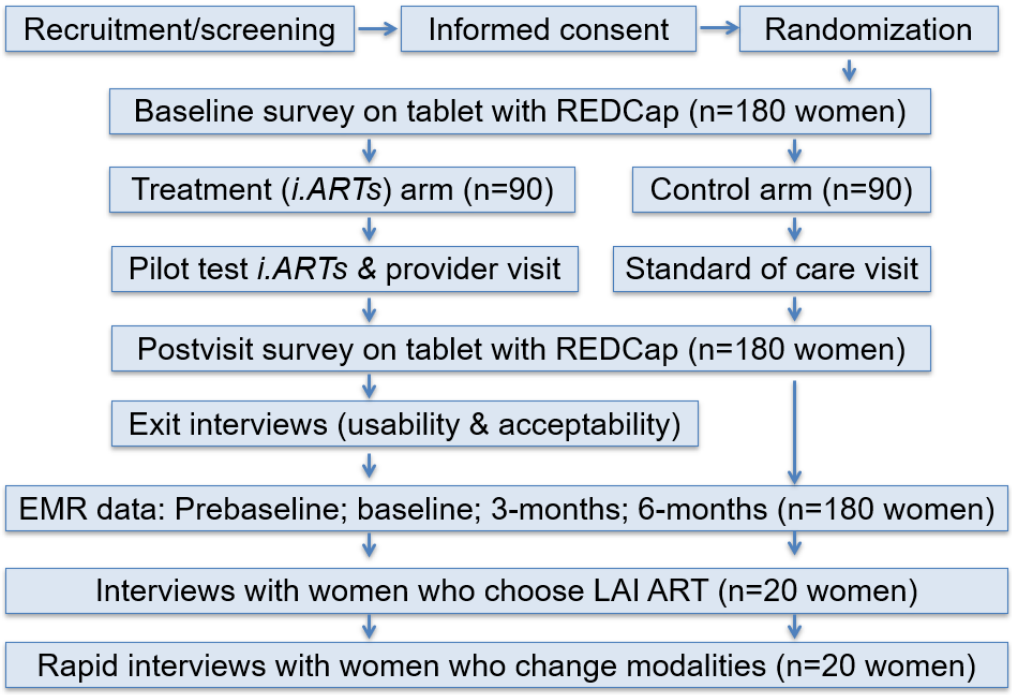


Figure 3. Pilot study flow and assessments. EMR: electronic medical record; *iARTs*: i.ART+support; LAI ART: long-acting injectable antiretroviral therapy.



Phase 3: Pilot Test *i.ARTs*

Study Design

Phase 3 will pilot test the final *i.ARTs* patient decision aid to assess feasibility, acceptability, and usability as well as to evaluate associations between receipt of *i.ARTs* and ART adherence, including viral suppression, ART refills, chosen ART modality, and clinic attendance. The pilot will be a 2-arm randomized controlled trial with 180 WWH. It will compare an intervention arm (n=90 WWH) that uses the *i.ARTs* decision aid tool developed in phases 1 and 2 with a standard-of-care control arm (n=90 WWH).

Setting, Participants, Recruitment, and Enrollment

Pilot testing will occur among WWH at the same Miami MWCCS clinical site where phase 2 focus groups occurred. The clinic is one of the largest hospital-based clinics in Miami, a city with one of the highest rates of incident and prevalent HIV infections in the United States. We will recruit 180 women from the existing client population over the course of 15 months (about 12 women per month). A full-time research associate will approach potential participants at their regular clinic visit, share information about the study, and invite them to take part in eligibility screening. Participants must meet the following eligibility criteria: (1) identify as female; (2) be receiving HIV-related care at the Miami site; (3) have a diagnosis of HIV infection; (4) aged 18 and older; (5) be interested in learning about LAI ART and open to discussing HIV treatment with their provider; and (6) be willing to provide informed consent.

Study Procedures

Randomization

Following informed consent and the baseline assessment (discussed later), we will use a web-based system to randomize women (1:1) to the *i.ARTs* intervention arm (n=90) or to the standard-of-care control arm (n=90). Neither participants nor researchers will be blind to study condition. Women in the control arm will receive standard of care as it exists at the time of LAI ART roll out: providers will offer women information about LAI ART and may strongly suggest which option she should choose. Women who participated in the focus groups will not be eligible for inclusion.

Women in the intervention arm will use *i.ARTs* as part of their regular participant visit. While the complete content of *i.ARTs* will be finalized in phase 2, the web-based *i.ARTs* app will guide WWH through the following activities: (1) provide education on different ART modalities, (2) utilize value clarification methods to guide women in ranking the prominence of relevant barriers and facilitators that may impact adherence to various ART modalities, (3) collect information on participant health history, (4) generate a suggested ART modality based on previous steps, (5) assist WWH in developing questions for their health care providers, and (6) generate an individual profile description as well as individualized suggestions to support adherence based on the modality selected (eg, a woman may be profiled as having transportation challenges; *i.ARTs* would suggest solutions—arranged transportation or transportation vouchers—that the clinic could employ to address these challenges). Participants will take a printout of this profile to their clinic visit with their provider. Intervention arm participants will receive US $15 for *i.ARTs* use.

Assessments

All women enrolled in the study will complete a baseline survey following informed consent and a follow-up survey immediately after their clinical visit. Surveys will be administered on tablets in a private room within the clinic and will use REDCap for data collection. Each survey will take approximately 25 minutes to complete, and women will receive US $25. Survey measures are described later and in Table 2.

A subsample of 20 intervention (*i.ARTs*) arm women and 10 providers will be randomly chosen to participate in an exit interview. This interview will occur either at the baseline visit or up to 1 month after *i.ARTs* use at the participant's convenience. We will select every fourth woman in the intervention arm to complete the exit interview. Providers will be selected based on the number of *i.ARTs* participants they served in the first year of the pilot (we will randomly select 10 providers from all providers who serve above the median number of *i.ARTs* clients, which ensures that providers will have sufficient experience with the tool to provide feedback) and exit interviews with providers will be conducted in the final 3 months of data collection. These interviews will focus on patient and provider experiences with *i.ARTs* acceptability, feasibility, and usability, and the most useful ways to improve its integration into clinical practice. This will also include discussions of how women shared the results from the patient decision aid with their provider. Exit interviews will take approximately 30 minutes and participants will be provided US $30 in compensation.

The study will also use all 180 participants' electronic medical records (EMRs) to assess the impact of the intervention on clinical outcomes (Table 2). The informed consent process will include the EMR abstraction release form and detailed information about the data abstraction process. Study staff will abstract data on viral suppression (all women), ART modality, clinic attendance (all women), and medication refill data (women on oral ART) from EMRs into a REDCap database. Abstraction will include data from 1-year prebaseline to 6 months postbaseline. This timeline is based on the frequency of HIV clinic visits (ie, approximately every 3 months) to ensure that women have at least one visit in the follow-up period.

Table 2. *i.ARTs*[a] pilot study measures in phase 3.

Outcomes	Description of measures
Primary	Assessed after *i.ARTs* use among women using i.ARTs (n=90)
Feasibility	Adaptation of Thabane et al's [59] framework [60,61] for assessing pilot studies: Process, Resources, Management, Science
Acceptability and usability	Acceptability [62] and CSQ-8[b] [63] to measure satisfaction with *i.ARTs*; exit interviews about *i.ARTs* features/protocol [62]
Secondary	Assessed in baseline survey and postvisit survey for all women (n=180)
Decisional conflict	Decisional Conflict Scale (16 items) [52]; satisfaction with the chosen method [64]
Tertiary	Assessed 1-year prebaseline, at baseline, 3 months, and 6 months (all women; n=180)
Viral suppression	Viral suppression, defined as viral load below limit of detection per assay used
Medication refills	Missed doses; report of medication refills/pharmacy pick up (WWH[c] on oral ART[d])
Clinic attendance	Missed or cancelled medical visits (<2 visits in a 6-month period for oral ART; missed monthly visit for LAI[e] ART)
ART modality	Adoption of LAI among patients who are virally suppressed
Moderators	Assessed at baseline
Sociodemographics	Race/ethnicity, age, housing stability, education, employment, income, distance from clinic, relationship status, children
Depression/anxiety	PHQ-8[f] (depression) [65]; GAD-7[g] [66]
Substance use	ASSIST[h] [67], an 8-item measure of problematic substance use
Stigma/discrimination	MDS[i] to measure racial discrimination [68]; HIV-related stigma
Self-efficacy	HIV-ASES[j] [38]
ART-related knowledge	Adaptation of Feldman's [69] scale of oral ART knowledge; BMQ[k] [70]

[a]*i.ARTs*: i.ART+support.
[b]CSQ-8: 8-item Client Satisfaction Questionnaire.
[c]WWH: women with HIV.
[d]ART: antiretroviral therapy.
[e]LAI: long-acting injectable.
[f]PHQ-8: 8-item Patient Health Questionnaire.
[g]GAD-7: 7-item General Anxiety Disorder scale.
[h]ASSIST: Alcohol, Smoking and Substance Involvement Screening Test.
[i]MDS: 10-item Multiple Discrimination Scale.
[j]HIV-ASES: HIV Treatment Adherence Self-Efficacy Scale.
[k]BMQ-18: 18-item Beliefs and Medicines Questionnaire.

Study Outcomes and Measures

All study outcomes are summarized in Table 2. *Primary outcomes* include *i.ARTs feasibility, acceptability,* and *usability.* To assess feasibility, we will adapt Thabane et al's [59] framework [60,61]. For *acceptability and usability,* we will use the 8-item Client Satisfaction Questionnaire (CSQ-8) to assess participants' attitudes, burden, ethics, coherence, opportunity cost, perceived effectiveness, and self-efficacy [63]. The *secondary outcome* is ART-related decisional conflict, a 16-item scale scored from 0 to 100 [52]. Scores of 0-25 are associated with "implementing decisions" and scores of 37.5-100 are associated with "decision delay/feeling unsure." *Tertiary outcomes* are exploratory, and consist of information extracted from EMRs, including viral suppression at the most recent visit in the prior 6 months, ART modality, medication refills (oral ART), and clinic attendance in the prior 6 months.

In addition to the outcomes, the baseline survey will measure moderators associated with adherence, including sociodemographics, depression, anxiety, substance use, HIV-related stigma and discrimination, self-efficacy, and ART-related knowledge.

Analysis

The primary outcomes of feasibility, acceptability, and usability will be assessed descriptively. We will compare ART-related decisional conflict, clinic attendance, viral suppression, and medication refills between and within the 90 women in each arm (baseline vs postvisit surveys and EMR data at 3 and 6 months). For normally distributed data, we will first use *t* tests

to compare the 2 arms and then use regression methods to develop a multivariable model of the outcome, with arm membership as the principal covariate, while controlling for the moderators listed in the previous sections and in Table 2. For nonnormally distributed data, we will employ chi-square tests and logistic regression; distributional properties of the outcome will determine the type of logistic regression (eg, binary, multinomial, or ordinal logistic regression models). We note that these are examples and the final approach will be determined based on the distribution of the data.

The primary analysis will use an intent-to-treat approach with the use of *i.ARTs* as a 1-time exposure, with α=.05, and 2-sided tests. The number of moderators included in the regression model will be used to make a Bonferroni adjustment to the α value. A secondary efficacy analysis will explore actual treatment taken. Our exploratory tertiary outcomes of viral suppression, clinic attendance, chosen ART modality, and medication refills will compare both between and within *i.ARTs* and control arm women (ie, baseline and postvisit surveys and EMR data at 3 and 6 months); we will also examine these outcomes for women who do not change regimens. We will use prebaseline EMR data to control for previous viral load. We will also compare how many women in each arm change modalities postbaseline to assess *i.ARTs'* accuracy in identifying which HIV treatment modality is the best match. Sensitivity analyses will determine whether assumptions associated with each model are defensible.

Power Analysis and Sample Size

Our sample size is based on our secondary outcome of decisional conflict, as our primary outcomes of acceptability and feasibility are only assessed in the intervention group (as the control group will not experience *i.ARTs*). Scale developers use a moderate effect size (0.3-0.4) to determine sample size. Using the average weighted means and SDs from prior studies [52], we calculated sample size for α=.05, power=0.8 for an independent samples *t* test. Assuming a mean score of 21 (SD 16) in the intervention (*i.ARTs*) group and a mean score of 28 (SD 18) in the control group, the sample size of 90 in each group, for a total of 180, provides 80% power. Our tertiary outcomes are exploratory, but as 35% of US women are not adherent after 6 months, we are powered to detect basic differences between the intervention and control arms.

Ethics Approval

This study received approval from the Columbia University Institutional Review Board (IRB; approval number IRB-AAAT5314), and we will receive approval from University of Miami IRB once the clinical trial portion begins.

Results

This study was funded in March 2021. Protocols for phase 1 interviews have been developed and interviews with service providers started in September 2021. We will apply for Clinicaltrials.gov registration prior to phase 3, which is when our first participant will be enrolled in the randomized controlled trial. This is anticipated to occur in April 2023.

Discussion

Research Implications

This paper describes the protocol for developing and piloting the first decision aid to facilitate women's decision making between LAI and oral ART modality for HIV treatment. This study will expand HIV treatment research in important ways. The field of HIV care has increasingly emphasized patient-centered care [42], as this approach improves quality of life, patient adherence, and health outcomes [28,42,71]. Patient decision aids are a key tool for patient-centered care, as they can enhance equity in medicine, activate patients to increase their knowledge and decision-making power, and lower medical paternalism [24,29-31]. They also enhance patient care by enabling shared discussions and outcomes that match patients' needs [26,42,72].

As noted, patient decision aids have been successfully used in other areas of medicine, most similarly to this in facilitating contraception decision making among women [40,41]. However, as yet no patient decision aids exist to facilitate the decision-making process between oral and LAI HIV treatment. Thus, *i.ARTs* is urgently needed to promote equity in patient-provider decision making by helping WWH identify their preferences for oral or LAI ART. Further, developing *i.ARTs* specifically for women may help promote gender equity in the uptake of LAI ART. Examples from oral pre-exposure prophylaxis (PrEP) scale up show that a lack of decision aid tools can hinder uptake and lead to gender-related disparities [73-76]. Women not only have much lower rates of PrEP use than men but also have shorter periods of sustained PrEP use [75,77,78]. Our study to develop and pilot test the *i.ARTs* patient decision aid aims to prevent a similar gender gap for LAI ART uptake and thus a further exacerbation of disparities in care and treatment outcomes.

Furthermore, this study comes at a crucial moment in HIV treatment. As the menu of options for ART treatment expands, patients and providers will encounter different considerations and concerns regarding the various ART modalities. Despite LAI ART's potential, we know little about the "real-world" facilitators and barriers WWH will face, or how providers will decide to whom to offer LAI ART. The FDA approved LAI ART in January 2021, and developing *i.ARTs* as LAI ART is rolled out has the potential to capture and address some of these real-world barriers and facilitators. In turn, it will provide data that can support the further dissemination of this new biomedical technology. In addition, *i.ARTs* can be updated to incorporate future ART modalities (eg, monthly oral medication [79,80], implants [81], subcutaneous injections [82]).

Study Strengths

Our study has multiple strengths that ensure the validity and applicability of its findings. As described in the previous sections, we incorporate patient and provider perspectives throughout *i.ARTs* development (phase 1, phase 2) and testing (exit interviews in phase 3). This ensures that *i.ARTs* content includes the full landscape of factors that influence LAI ART uptake, determine whether LAI or oral ART best fits a woman's values and preferences, and will help us to identify potential

differences in patient and providers' beliefs regarding who should be offered LAI ART.

Next, our real-world clinic-based sample can provide insight into LAI ART uptake that samples of clinical trials participants cannot. As mentioned, women were underrepresented in LAI ART clinical trials [10-13]. Working with women from the MWCCS not only resolves this gender gap, but also provides data that trial- and clinic-based samples (eg, CFAR Network of Integrated Clinical Systems [CNICS] sites) cannot, as it includes out-of-care women who may face different and additional adherence barriers. Clinical trials include participants with high adherence to determine drug efficacy, but only 49% of MWCCS women would be eligible for AIDS Clinical Trials Group trials [44]. Furthermore, pilot testing *i.ARTs* in Miami, which leads the United States in HIV incidence, and whose HIV epidemic is marked by stark racial and ethnic disparities, will help us identify the full landscape of WWH's barriers to ART use and potential solutions to address them. This will increase the relevance of *i.ARTs* for WWH across the United States.

Finally, our study benefits from its mixed methods approach [83], which increases validity by capitalizing on each method's inherent strengths. The different methods answer complementary research questions: we will use the phase 1 survey and provider interviews to explore potential disconnects between who may be offered LAI ART and who wants it, which can affect patient equity; interviews with women who choose LAI ART will explore the mechanisms that drive viral suppression data abstracted from EMRs. We will integrate mixed method findings using "triangulation" (ie, use of 2 different methods to address the same research question) to improve reliability [84,85]. Consistency of findings across methodological approaches increases validity and reliability and suggests findings are not due to methodological artifacts [86]. This will allow us to see how themes vary across methods, leading to stronger findings than using each method independently.

Expected Challenges

As this study is set in real-world clinical settings, we expect challenges to incorporating *i.ARTs* delivery into existing clinical workflows. These include considerations such as available space for participants to complete *i.ARTs*, tech support for the computerized tool and printout, staffing resources, and limited clinician time with each patient to discuss the decision aid results. The study team will work with the clinic staff to determine how to ensure efficient delivery of *i.ARTs* in the clinical setting. Exit interviews will be used to collect data on these challenges to inform further scale-up or dissemination efforts of *i.ARTs* outside of the Miami-based clinic.

As LAI ART is being administered in a real-world setting, participating clinicians are subject to existing, and possibly changing, FDA approvals. While phase 3 trials are currently testing LAI ART for nonadherent patients, *the FDA-approved LAI ART formulation is only for virally suppressed patients*. To ensure *i.ARTs* incorporates all relevant drivers of ART use for all women, we aim to include nonadherent women in aim 3, pending FDA approval. If FDA approval only exists for virally suppressed WWH when aim 3 starts, then we will limit the pilot test to that population. Should FDA approval for nonadherent patients begin in the middle of the pilot, we may adjust eligibility criteria to ensure a standard participant population throughout the pilot period. The study team will carefully monitor developments in ART treatment technologies and adapt accordingly. In addition, LAI ART was initially approved as a monthly injection, and the US FDA has approved a bimonthly (ie, every 8 weeks) formulation of LAI ART. This may also affect women's preferences as the study is rolled out.

New modalities of ART delivery may emerge prior to the pilot study period, including monthly oral medication [79,80], implants [81], and subcutaneous injections [82]. The addition of these new technologies could further complicate the decision-making process. As mentioned earlier, the *i.ARTs* tool is web based and thus easy to update as technology or treatment modalities change [87]. The web-based nature of this tool will allow us to adapt and expand *i.ARTs* to all genders in future studies. In addition, a similar approach could be used to develop a tool to facilitate women's decision-making process between oral and LAI versions of PrEP, with a goal to limit HIV infections among women.

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Authors' Contributions

MMP, MA, MP, and VAS conceptualized the study and the methodology. MMP, MP, and VAS contributed to the statistical analysis plan. TM and MMP wrote the original manuscript. All authors reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

AAA has received personal funds from Merck, Viiv, and Gilead for consulting; her institution has received funding from Merck and Gilead for her research.

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Abbreviations

ART: antiretroviral therapy
CNICS: CFAR Network of Integrated Clinical Systems
EMR: electronic medical record
FDA: Food and Drug Administration
***i.ARTs*:** i.ART+support
IPDAS: International Patient Decision Aids Standards Collaboration
IRB: institutional review board
LAI ART: long-acting injectable ART
MWCCS: MACS/WIHS Combined Cohort Study
PrEP: pre-exposure prophylaxis
WWH: women with HIV

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Protocol

Bronchopulmonary Penetration of Isavuconazole in Pulmonary Transplant Recipients (PBISA01): Protocol for a Phase IV Clinical Trial With a Single Treatment Arm

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Abstract

Background: Aspergillosis is the most frequently observed invasive fungal disease (IFD) in lung transplant recipients. Isavuconazole (ISA) has shown a better safety profile and noninferiority to voriconazole in the treatment of patients with IFD.

Objective: The aim of this study is to describe the bronchopulmonary pharmacokinetic profile of oral ISA by analyzing the degree of penetration in the epithelial lining fluid and alveolar macrophages in patients receiving lung transplantation with a diagnosis of IFD.

Methods: A total of 12 patients aged ≥18 years receiving a lung transplant with an IFD diagnosis and indication for ISA treatment and follow-up bronchoscopy will be included in the study. After 5 days of treatment with ISA and before the treatment is discontinued, the patients will be randomized (1:1:1:1) to perform the scheduled bronchoscopy at various times after the administration of ISA (2, 4, 8, and 12 hours). In total, 4 blood samples will be obtained per patient: at 72 hours after treatment initiation, on the day of the bronchoscopy, at the time of the bronchoalveolar lavage (simultaneously), and at 7 days after treatment initiation, to analyze tacrolimus and ISA plasma levels. ISA concentrations will be measured in plasma, epithelial lining fluid, and alveolar macrophages by a high-performance liquid chromatography/UV coupled to fluorescence method.

Results: Enrollment for the PBISA01 trial began in October 2020 and was completed in October 2021. All samples will be analyzed once recruitment is complete, and the results are expected to be published in October 2022.

Conclusions: There are no clinical studies that analyze the bronchopulmonary penetration of ISA. Bronchoalveolar lavage performed routinely in the follow-up of lung transplant recipients constitutes an opportunity to analyze the bronchopulmonary penetration of ISA.

Trial Registration: European Clinical Trials Register 2019-004240-30; www.clinicaltrialsregister.eu/ctr-search/trial/2019-004240-30/ES

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KEYWORDS

isavuconazole; triazoles; invasive fungal infections; fungus; fungal; infection; pharmacokinetic; bronchoalveolar lavage; bronchoalveolar lavage fluid; bronchoscopy; lung transplant; bronchopulmonary level; bronchopulmonary; epithelial lining fluid; bronchiole; alveolar macrophage; pharmaceutical; drug efficacy

Introduction

Background

Invasive fungal diseases (IFDs) are a frequent cause of morbidity and mortality in solid-organ transplant recipients. Lung transplant recipients are especially vulnerable to the development of these infections as a result of the peculiarities of the pulmonary graft, permanent contact with the external environment, and the high levels of immunosuppression necessary for the prevention of rejection [1]. Aspergillosis is the most frequently observed IFD in lung transplant recipients [2]. Despite the universal prophylaxis with voriconazole and nebulized amphotericin B, a nonnegligible percentage of patients present with *Aspergillus* infection [3,4]. The period of greatest risk is immediately posttransplant. However, the risk is maintained throughout the posttransplant evolution.

Triazoles are effective drugs against *Aspergillus* infection. Voriconazole is the drug of first choice for the treatment of invasive aspergillosis [5,6]. However, it is not free of adverse effects.

Isavuconazole (ISA) is indicated in adults for the treatment of invasive aspergillosis and mucormycosis in patients for whom amphotericin B is inappropriate. ISA has shown a better safety profile and noninferiority to voriconazole in the treatment of patients with IFD [7] and is being increasingly used. Data from healthy volunteers demonstrated high oral bioavailability, high hepatic metabolism, and an extended elimination half-life [8].

The efficacy of ISA depends on fungal exposure to the drug and the minimum inhibitory concentration of the microorganism. To achieve the desired therapeutic effect in lung infections, it is necessary to ensure that the drug penetrates properly at the bronchopulmonary level. As it has already been shown for other azoles [9-11], the properties of ISA will greatly determine its distribution to tissues, organs, compartments, and fluids [12].

There are no clinical studies that analyze the bronchopulmonary penetration of ISA.

In this sense, the bronchoalveolar lavage (BAL) performed routinely in the follow-up of lung transplant recipients constitutes an opportunity to analyze the bronchopulmonary penetration of ISA. The simultaneous determination of the levels of ISA in plasma and the epithelial lining fluid (ELF) obtained through the BAL can be useful to determine its penetration at the bronchopulmonary level and correlate it with the response to treatment [13]. This aspect is especially relevant as lung transplant recipients are a population that is especially susceptible to the development of IFD.

Goal of the Study

The aim of this study is to describe the pharmacokinetic profile of oral ISA at the bronchopulmonary level through the degree of penetration in the ELF in patients receiving lung transplantation with a diagnosis of IFD.

Methods

Design

This is a single-center, phase IV, prospective, noncontrolled, open-label, and single-arm clinical trial aimed at describing the pharmacokinetic profile of oral ISA at the bronchopulmonary level. This will be done through analyzing the degree of penetration in the ELF from lung transplant recipients diagnosed with IFD. A total of 12 patients aged ≥18 years receiving a lung transplant with an IFD diagnosis and indication for ISA treatment according to the Summary of Product Characteristics will be included in the study.

This clinical trial has been registered on the European Clinical Trials Register (2019-004240-30). This study will adhere to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement (see Figure 1 for the SPIRIT figure of enrollment, interventions, and assessments and Multimedia Appendix 1 for the SPIRIT checklist).

Figure 1. Schedule of enrollment, interventions, and assessments. ELF: epithelial lining fluid.

		Study period						
		Enrollment	Allocation	Postallocation				Closeout
Timepoint (days)		−1 to 0	0	1	4	5	7	15
Enrollment								
	Eligibility screen	✓						
	Informed consent	✓						
	Allocation		✓					
Interventions								
	Treatment administration		←	—	—	—	—	→
	Bronchoalveolar lavage					✓		
	Blood test		←	—	—	—	—	→
Assessments								
	Plasma and ELF concentration of drugs			✓	✓	✓	✓	
	Pharmacokinetic interaction of isavuconazole with immunosuppressive drugs							✓
	Adverse events			✓	✓	✓	✓	✓

Ethics Approval

This study will be carried out in accordance with the principles emanating from the Declaration of Helsinki (2013) and the Oviedo Convention of the Council of Europe of 1997, ratified in 1999, and according to current legal regulations in Spain (Royal Decree 1090/2015 and EU Clinical Trials Regulation 536/2014).

The project, the final amended protocol (version 1; October 31, 2019), and the consent form have been reviewed and approved by the Research Ethics Committee at Hospital Universitario Puerta de Hierro-Majadahonda (approval 167/19) and the Spanish Regulatory Authority (Spanish Agency of Medicines and Medical Devices).

Eligible patients may only participate in the study after providing written informed consent approved by the Research Ethics Committee.

Informed consent must be obtained before performing any specific study procedure. The process of obtaining informed consent should be documented in the patient's source documents (medical history).

Participants and Recruitment

The patients will consecutively be enrolled from October 2020 to June 2022 in Hospital Universitario Puerta de Hierro-Majadahonda. All the patients will be hospitalized.

Before enrollment, participants will be provided with detailed information about the clinical study, including its purpose, processing, scheduling, and possible risks and benefits. All patients will be required to sign an informed written consent before any study procedures commence.

Sample Size

In total, the inclusion of 12 lung transplant recipients is planned. Currently, there are no data in the scientific literature about the pulmonary disposition of ISA. The number of subjects has been estimated based on the objective and characteristics of the study and the drug under study. Given the descriptive nature of the study and previous similar studies [9,10], it has been considered that with the exposure of 12 subjects, the precision of the estimates will be sufficient to determine the pharmacokinetic profile of oral ISA at the bronchopulmonary level.

Patients eligible for inclusion in this study must meet all the inclusion criteria and should not meet any of the exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Recipient of a lung transplant, aged ≥18 years, with an indication of treatment with isavuconazole according to the Summary of Product Characteristics
- No limit between the date of transplant and the date of onset of the fungal infection requiring treatment with isavuconazole
- Intent and ability to follow scheduled visits, treatment plan, laboratory analysis, and other study procedures
- Legally competent and able to understand, sign, and date the informed consent form
- Signing of the written informed consent in accordance with Good Clinical Practice and local legislation, obtained before any study procedure

Exclusion criteria

- Allergy or intolerance to isavuconazole
- Contraindication for bronchoscopy or bronchoalveolar lavage
- Any clinical condition or analytical disorder that, in the opinion of the investigator, are considered clinically relevant to participate in the study
- Individuals who show an inability to follow the instructions or collaborate during the study
- Women who are pregnant or undergoing breastfeeding
- Having participated in another clinical trial during the 3 months prior to the start of the study in which a research or commercially available drug was tested
- Lack of intent or inability to follow the procedures described in the protocol
- Inability to grant written informed consent

Intervention

The trial has been approved as a "low interventional clinical trial" according to the definition in the European Clinical Trials Regulation (536/2014), because the investigational medicinal product is used in accordance with the terms of the marketing authorization, and the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

All participants included will receive the product under investigation—oral ISA—at the doses and dosage regimen stated in the Summary of Product Characteristics: loading dose of 200 mg/8 h for the first 48 hours and maintenance dose from day 3 at 200 mg/24 h.

After 5 days of treatment with ISA and before the treatment is discontinued, patients will be randomized to perform the scheduled bronchoscopy at different times from the administration of ISA with the following distribution:

- Group 1 (n=3): 2 hours from the administration of ISA
- Group 2 (n=3): 4 hours from the administration of ISA
- Group 3 (n=3): 8 hours from the administration of ISA
- Group 4 (n=3): 12 hours from the administration of ISA

Furthermore, 4 blood samples will be obtained per patient: at 72 hours after treatment initiation, on the day of the bronchoscopy, at the time of the BAL (simultaneously), and at 7 days after treatment initiation, to analyze tacrolimus and ISA plasma levels.

There is no restriction regarding the use of medications and concomitant therapies. All medications (except study medication) and nondrug therapies administered during the study should be listed in the corresponding section of the concomitant medication case report form (CRF). The use of any concomitant treatment will be carried out according to the authorized conditions of use or, failing that, according to the usual clinical practice.

Outcome Measures

Primary End Point

The primary outcome is the measurement of ISA in the ELF. ISA concentrations will be measured in plasma ELF and alveolar macrophages by a high-performance liquid chromatography/UV coupled to fluorescence method. ISA levels in the ELF and alveolar macrophages will be obtained from the BAL. The proposed chromatographic method will allow the quantification of ISA in the clinical samples after a first step of protein precipitation and the direct injection (plasma) of resulting supernatant. For BAL samples, a previous step of sample concentration will be required to increase the sensitivity of the method. The analytical run will result in the specific characterization and robust quantification of this triazole by its UV and fluorescent profile.

Data from the cell count, percentage of alveolar cells, and volume of cell-lining fluid will be presented for the different times when bronchoscopy is performed. The volume of cell-lining fluid will be estimated using the concentration of urea in plasma and BAL from the following formula [13]: *estimated ELF volume = amount of total urea in BAL (mg) / plasma urea concentration (mg/mL)*. The area under the curve of ISA will be estimated at the ELF level. The concentration, time-dependent curves in the ELF will be calculated using noncompartmental analyses. The ratio between the ELF and plasma will be estimated from the average values of the patients included in each group.

Secondary End Points

For interaction evaluation, tacrolimus and mycophenolate concentrations will be determined before treatment and at 72 hours, 96 hours, and 7 days from the initiation of ISA treatment. The percentage of patients who required dose adjustment of the immunosuppressive drug after the start of treatment with ISA and the magnitude of the adjustment will be determined.

Safety will be assessed by recording adverse effects, the physical examination of patients, and analytical results.

A systematic description of all adverse events recorded during the follow-up will be performed. Listings of adverse events, previously coded by the Medical Dictionary for Regulatory Activities and grouped by organ or systems according to severity, intensity, and causal relationship with the study medicinal products, will be included.

Adverse Events

From the signing of informed consent to the end of the study, all adverse events that the investigator considers related to the study procedures will be recorded.

As part of the medical history, health problems (including clinically significant vital analytical values or constants located outside the reference range) that were diagnosed or known before the signing of informed consent will be recorded.

Data Management and Quality Control

All records will be collected in a CRF, which will be completed by a trained and qualified investigator. Once a CRF is completed, the original record will not be changed if any corrections are made. The completed CRF will be reviewed by the clinical monitor.

Data entry and management will be guided by medical statistics experts. After reviewing and confirming that the established database is correct, the data will be locked by the main researchers and statistical analysts. The locked data or files will not be changed thereafter and will be submitted for statistical analysis by the research group. The Clinical Trial Unit of Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana, which does not have any competing interests, will be responsible for monitoring the data.

The study will be safely conducted in accordance with the protocol and applicable regulatory requirements under Good Clinical Practice, and data collection will be properly executed.

Statistical Analysis

The statistical analysis will be carried out following the principles specified in the International Conference on Harmonization Topic E9 (CPMP/ICH/363/96). The data will be analyzed using the SPSS statistical software (version 22.0; IBM Corp).

Given the characteristics of the study—a descriptive study—only 2 analysis groups are planned: (1) the safety and tolerability analysis group, which will include all patients who have received at least 1 dose of ISA; and (2) the pharmacokinetic analysis group, which will include all patients with BAL samples from bronchoscopy.

Demographic data and other data related to patient selection will be descriptively summarized for the pharmacokinetic analysis group and the safety and tolerability group. Categorical data will be presented in the form of frequencies and percentages. For continuous data, descriptive statistics such as mean, median, and SD or median, IQR, minimum, and maximum will be presented.

Results

The enrollment for the PBISA01 trial began in October 2020 and was completed in October 2021. Thirteen patients have been enrolled in this clinical trial. No data regarding the pharmacokinetic profile of ISA has been analyzed yet. The results are expected to be published in October 2022.

Discussion

Expected Findings

There are no clinical studies that analyze the bronchopulmonary penetration of ISA. Our hypothesis is that the bronchopulmonary penetration of ISA in lung transplant recipients may be compromised as a result of poor vascularization and local inflammatory phenomena.

In this sense, the BAL performed routinely in the follow-up of lung transplant recipients constitutes an opportunity to analyze the bronchopulmonary penetration of ISA. The simultaneous determination of the levels of ISA in plasma and the ELF obtained through the BAL can be useful to determine its penetration at the bronchopulmonary level and correlate it with the response to treatment [13]. This aspect is especially relevant as the lung transplant recipients are a population that is especially susceptible to the development of IFD.

The use of BAL samples as surrogates of ELF and alveolar macrophages exposure of ISA requires the development of a sensitive method of analysis. The proposed chromatographic method includes one important advantage: the dual detection of UV and fluorescence. The fluorescence detection results in sensitivities between 1 and 3 orders of magnitude higher than absorption methods.

It is well-accepted that penetration into the site of infection to achieve microbe-eliminating concentrations is a key requirement for the efficacy of all antimicrobial agents [14]. The concentration of ISA within the lung ELF may provide a good estimate of drug exposure for the treatment of IFD [12]. However, the monitoring of ISA concentration in the ELF via bronchoscopy is not practical in the clinical setting, so the use of plasma ISA concentration as a surrogate for the ELF concentration is a good alternative.

The pharmacokinetics of ISA has been studied as an experimental treatment of invasive aspergillosis in neutropenic rats. In one study [15], the subjects treated with ISA had a lower residual fungal load after treatment, lower lung damage, greater survival, and lower levels of (1,3)-β-D-glucan, both in plasma and the BAL.

Other physiological factors such as the presence of inflammation and changes in vascularization substantially influence the

exposure of drugs at the site of action. This aspect is especially relevant in the lung transplant recipient in which the absence of bronchial revascularization and local inflammatory phenomena secondary to ischemia and reperfusion can hinder the tissue penetration of drugs.

The design of the study includes the randomization of the patients to perform the scheduled bronchoscopy at different times after dose intake. This is a suitable design to collect ISA pulmonary concentration at different timepoints without interfering with the scheduled dosage and with no additional burden to the patient. The number of subjects has been estimated based on the objective and characteristics of the study and the drug under study. Given the descriptive nature of the study and previous similar studies [9-11], it has been considered that with an exposure of 12 subjects, the precision of the estimates will be sufficient to determine the pharmacokinetic profile of oral ISA at the bronchopulmonary level.

Conclusions

To the best of our knowledge, this study will be the first well-designed clinical trial to analyze the bronchopulmonary penetration of ISA in a steady-state situation in patients receiving a lung transplant.

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PBISA01-study group collaborators: Cristina López García-Gallo, Gemma Díaz Nuevo, Rosalía Laporta Hernández, Maite Lázaro-Carrasco de la Fuente, Teresa Merino, Cristina Armentia.

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Authors' Contributions

IDX, AFCB, BRA, PUG, ASL, AGL, and MAP conceptualized the study. PUG, IDX, AFCB, BRA, MAP, AGL, ASL, CGF, EDS, MVF, and CAS were involved with the investigation. BRA, PUG, and CAS supervised the study. IDX and AFCB wrote the original draft. AFCB, BRA, MAP, AGL, ASL, CGF, EDS, MVF, PUG, and CAS reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 74 KB - resprot_v11i9e37275_app1.pdf]

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Abbreviations

BAL: bronchoalveolar lavage
CRF: case report form
ELF: epithelial lining fluid
IFD: invasive fungal disease
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Digital Peer Support Platform to Translate Web-Based Peer Support for Emerging Adult Mental Well-being: Protocol for a Randomized Controlled Trial

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Abstract

Background: Mental health issues among emerging adults (aged 19-25 years) on a global scale have underscored the need to address their widespread experiences of depression and anxiety. As a result of the COVID-19 pandemic, emerging studies are being directed toward the development and deployment of digital peer emotional disclosure and support for the psychological well-being of emerging adults. However, it is important to explore the implementation and clinical effectiveness, as well as associated mechanisms of change, for optimal approaches in conducting digital peer support interventions for emerging adults' psychological well-being.

Objective: We describe a randomized controlled trial to evaluate the implementation and clinical effectiveness of Acceset, a digital peer support intervention to address emerging adult mental well-being. The intervention has 2 components. First, the digital peer support training equips befrienders (ie, peers who provide support) to harness 4 components of psychological well-being—mattering, selfhood, compassion, and mindfulness—to provide effective peer support for seekers (ie, peers who seek support). Second, Acceset incorporates psychological well-being digital markers and harnesses community engagement to drive emotional disclosure among peers.

Methods: A total of 100 participants (aged 19-25 years) from the National University of Singapore will be recruited and randomized into 2 arms. In arm 1 (n=50), the seekers will use Acceset with befrienders (n=30) as well as moderators (n=30) for 3 weeks. Arm 2 comprises a wait-listed control group (n=50). A questionnaire battery will be used to monitor seekers and befrienders at 4 time points. These include baseline (before the intervention), 3 weeks (end of the intervention), and 6 and 9 weeks (carryover effect measurement). Implementation outcomes of the intervention will involve evaluation of the training curriculum with respect to adoption and fidelity as well as user acceptability of the Acceset platform and its feasibility for broader deployment. Clinical outcomes will include mattering, selfhood, compassion, mindfulness, perceived social support, and psychological well-being scores.

Results: This protocol received National University of Singapore Institutional Ethics Review Board approval in October 2021. Recruitment will commence in January 2022. We expect data collection and analyses to be completed in June 2022. Preliminary findings are expected to be published in December 2022. The Cohen *d* index will be used for effect size estimation with a .05 (95% reliability) significance level and 80% power.

Conclusions: This protocol considers a novel digital peer support intervention—Acceset—that incorporates components and digital markers of emerging adult mental well-being. Through the validation of the Acceset intervention, this study defines the parameters and conditions for digital peer support interventions for emerging adults.

Trial Registration: ClinicalTrials.gov NCT05083676; https://clinicaltrials.gov/ct2/show/NCT05083676

International Registered Report Identifier (IRRID): PRR1-10.2196/34602

(JMIR Res Protoc 2022;11(9):e34602) doi:10.2196/34602

KEYWORDS

mental health; digital health; peer support intervention; peer emotional disclosure; randomized controlled trial

Introduction

Background and Rationale

Emerging adulthood is a development phase that spans the ages of 19 to 25 years in most high-income economies [1]. This developmental period is marked by unique challenges as emerging adults negotiate different features such as identity exploration and feelings of instability [1]. The uncertainty that accompanies the numerous changes and the substantial fluctuations in positive and negative emotional states during this developmental period result in widespread experiences of anxiety and depressed moods [1]. The global rise in mental health issues among emerging adults has fueled concerns regarding emotional distress, including depression, anxiety, and coping mechanisms [1]. This prepandemic emotional distress has been compounded by the outbreak of COVID-19, which has brought about prolonged isolation and reduced social connections [2-4]. With the unprecedented developmental implications associated with the pandemic most directly felt by college students negotiating emerging adulthood, there is a growing need to understand how to support the mental well-being of these young individuals [5,6].

Emerging studies are showing that digital peer support may effectively address the mental well-being of young people [7,8]. Digital communication has been prevalent among emerging adults even before the pandemic [9,10] and, with the onset of the pandemic, digital peer connections have become even more pervasive and important among college students as a coping mechanism to manage emotional experiences and distress [2]. Among college students, disclosure over digital communication channels is the norm for building relational closeness [11]. The collective experiences of managing intensifying concerns and intense negative feelings associated with the onset of the pandemic has driven college students' social connections on the web [5,6], particularly the use of digital platforms for peer emotional sharing [2]. According to the social sharing of emotions framework, emotional disclosure on the web functions as a psychological mechanism for managing emotional lability and distress, which leads to emotional regulation and recovery [12,13]. However, it is important to increase our understanding of the ideal workflow for implementing digital peer emotional disclosure and support as an intervention [7,8], how to achieve relevant clinical outcomes, and the assessment of associated mechanisms of change. Therefore, it is essential to assess the efficacy of web-based peer emotional disclosure and support systems as well as the mechanisms of change.

Importance of Digital Peer Emotional Disclosure and Support With the Onset of the COVID-19 Pandemic

According to the social sharing of emotions framework, emotional disclosure refers to the dyadic communication of significant and personal experiences with mild to strong positive and negative emotions with one's close social network [12-14]. It focuses on emotionally laden experiences (eg, *I was exhilarated to receive a good grade on an exam* or *I was distressed being involved in a car accident*) that are distinguished from impersonal experiences (eg, *Football games can be exciting*) and those that are mundane and void of emotional content (eg, *I went to town after school*) [12-14]. For emerging adults, peers are the primary target audience for emotional disclosure, which serves as a stress coping mechanism that facilitates emotional regulation and recovery [12-14].

With the increased prevalence of digital peer communication among emerging adults, this form of communication has the potential to facilitate and sustain relational closeness and relationship quality with friends in a scalable manner [15,16]. A possible mechanism is the social sharing of emotions as emerging adults commonly disclose their emotions through texting [17]. The importance of digital peer emotional disclosure has been heightened with the onset of the COVID-19 pandemic. The social implications of the COVID-19 pandemic, which involve uncertainty, insecurity, and a reduced sense of agency and self-directedness, have had a substantial impact on emerging adults, especially college students [18,19]. Emerging adults reported increased loneliness as social and physical distancing were implemented, and staying connected with peers through digital communication may buffer the feelings of loneliness [5,6]. For college students, their peer emotional disclosure on the web has been pivotal in managing the collective experiences of intensified concerns and intense negative feelings [2].

Emotional lability in adolescence, which stems from extensive biological and social changes in relational dynamics with parents and peers, extends into emerging adulthood as a consequence of negotiating a different set of developmental features that are new and challenging [20,21]. Studies have indicated that emerging adulthood is characterized by heightened fluctuations in emotional positivity (ie, the degree of positive emotional experiences) and negativity (ie, the degree of negative emotional experiences), which are associated with a greater propensity for anxiety and depression than in other developmental stages [1]. These normative experiences have been compounded with the onset of the pandemic. Studies have documented systematic decreases in positivity and increases in negativity that were

associated with COVID-19 among adolescents and college students [2-4]. These observations demonstrate the need to prioritize the development of mental health interventions for emerging adults.

Our review of the existing literature reveals a limited understanding of how dyadic emotional disclosure and support from friends can collectively function as a digital intervention in support of the mental well-being of emerging adults [8,22-24]. Before the pandemic, the administration of digital peer support to a college student population mediated the impact of various psychological and health outcomes [25,26]. With the onset of the global pandemic, the increase in social connections on the web underscores the potential effectiveness of digital peer emotional disclosure and support to positively affect the psychological well-being of college students [2,5,6]. Digital peer support platforms may address specific areas of well-being that include anxiety, depression, and suicidal ideation [24,27]. These findings have provided the impetus for researchers, education stakeholders, and health care professionals to understand the role of peer support on digital platforms in intervening in the psychological well-being of emerging adults, particularly college students. The subsequent initiation and completion of these studies are expected to yield insights into the implementation and feasibility outcomes, user acceptability of the interventions, and clinical effectiveness in addressing anxiety and depression among college students.

This Study

Overview

Research evidence indicates that interventions that successfully affect the mental well-being of emerging adults include the following elements: (1) multiple components; (2) community engagement; and (3) consultation with emerging adults on the co-design of the intervention in an effort to potentially increase adherence and sustained engagement with the platform, a critical element of scalable and effective interventions [8,28,29]. To this end, we worked with Acceset (Multimedia Appendix 1), a social enterprise that provides digital text-based intervention to harness the therapeutic potential of peer disclosure and support on the web for emerging adult mental well-being. Through Acceset, users (seekers) can anonymously share their emotional experiences and receive support from their peers (befrienders), who receive training in digital peer support skills from clinical psychologists and certified counselors (moderators). Aligned with the characteristics of successful interventions, Acceset has been designed as a digital peer support intervention that is multifaceted. It entails a digital peer support training curriculum and a digital text-based intervention, uses a community-based approach, and involves emerging adults in the design and trial process. In this study, Acceset is a stand-alone product that is used as an intervention platform.

The digital peer support training being validated in this study may serve as a comprehensive strategy built on anonymous human interaction to address mental well-being in that it harnesses 4 components of emerging adult mental well-being. Emerging literature on COVID-19 underscores the role of these components in alleviating emerging adults' psychological distress, including anxiety and depression [30-32]. These components include (1) enhancing one's sense of mattering (the extent to which we are important to the surrounding world and people), (2) strengthening selfhood (one's sense of identity and role), (3) exploring compassion (the degree of sensitivity to one's and others' pain and distress, with a desire to alleviate that pain and distress), and (4) cultivating mindfulness (paying attention to the present moment with intention and acceptance; refer to the Methods section for details). Our consultations and pilot trial of the Acceset intervention involving emerging adults from institutes of higher learning (IHLs) revealed findings that were consistent with the literature regarding how mattering, selfhood, compassion, and mindfulness can address the mental health challenges of college students [33], particularly during the global pandemic. The coding of the content from these emerging adults' lived experiences of mental health conditions, particularly their anxiety and depressive symptoms, revealed these 4 components that helped them manage mental health challenges (Multimedia Appendix 2). These preliminary findings provide evidence to harness the interventional potential of these 4 components in Acceset digital peer support training to build befrienders' capacity to deliver these ingredients to provide effective peer support to seekers.

The Acceset text-based intervention (ie, the platform) incorporates digital markers of psychological well-being—specifically, emotionality (ie, positivity and negativity), motivations, and functional adjustment (ie, internalizing and externalizing behaviors)—and hinges on the peer emotional disclosure process. These are markers of psychological well-being as emerging adults' emotional positivity and negativity, innate psychological motivations, and functional adjustment are important precedents and indicators of their well-being [1,34,35]. During the course of the digital peer interaction, when users engage with the features on the Acceset platform, they provide information about these markers, which is subsequently correlated with their self-report measures of mental well-being. These markers can shift during the course of interaction for longitudinal assessment of user mental well-being status and can potentially also stratify users toward follow-up engagement with additional mental health professionals and resources. Furthermore, the Acceset digital peer emotional disclosure and support process leverages the Singapore ecosystem and community to potentially form a web-based safety net. Designed to reduce fear and stigma, seekers (those who seek help anonymously) find help through the exchange of anonymous e-letters by disclosing the issues that bother them. By tapping on common lived experiences, the community (befrienders and moderators) relates authentically to the seeker and affirms the seeker's emotional experiences by giving dedicated attention to the issues with which they are confronted. As a key strategy for effective engagement with digital interventions is co-designing them [8,29,30], consultations with emerging adults aged 19 to 25 years from institutes of higher education in Singapore were conducted to curate these digital features.

Aims, Research Questions, and Hypotheses

The Acceset intervention addresses 3 gaps in the current research. First, our published work, undertaken to identify mobile health (mHealth) platforms across popular app stores

and academic databases, found 302 anxiety and depression mHealth platforms that are currently available [36]. Of note, most mHealth platforms on the market are not designed for a specific age group and, even of those used academically, only 13% are designed specifically for emerging adults. Second, despite preliminary literature that highlights the importance of digital intervention, particularly involving peer support, on emerging adults' psychological well-being, there is a continued need to achieve effective implementation strategies and clinical outcomes [24,27]. The increasing mental health issues that stem from prolonged isolation and reduced social connections associated with the outbreak of COVID-19 further the impetus among researchers, policy makers, and other stakeholders to design effective interventions that consider the need for users to access support remotely. To this end, a digital peer support intervention provides the desirable features of remote accessibility, which enables nonstrictly in-person mental health treatment options as well as remote monitoring access.

Third, notwithstanding the benefits of harnessing the components of mattering, selfhood, compassion, and mindfulness in promoting emerging adults' mental well-being, the proposed validation of these combined components for emerging adults' psychological well-being represents, to the best of our knowledge, a unique prospective study. A leap forward would be to test the feasibility of incorporating these components in an mHealth platform either as a stand-alone platform or as a combination intervention. Finally, in the absence of evidence demonstrating the mechanism of change relating digital peer support interventions to emerging adults' psychological symptoms, it is not clear whether or how digital peer support intervenes in the development of psychological symptoms or how they unfold over time. This information could potentially provide actionable knowledge for timely and relevant digital peer support interventions. To this end, this study is based on the aims and hypotheses outlined in Textbox 1.

Textbox 1. Aims and hypotheses of this study.

Aims and hypotheses

- Aim 1: the first aim is to evaluate the implementation effectiveness of digital peer support training between emerging adults providing support (befrienders) and emerging adults seeking help (seekers).
  - Research question 1a: is Acceset digital peer support training an effective training curriculum in providing peer support?
  - Hypothesis 1a: the digital peer support training is effective for befrienders in providing peer support, as demonstrated by the adoption of and fidelity to the training curriculum.
  - Research question 1b: is the Acceset text-based intervention (ie, the platform) feasible and acceptable (ie, safe and timely) as an ongoing mechanism of support for seekers and befrienders?
  - Hypothesis 1b: digital peer support is feasible and acceptable in offering support for emerging adults' mental well-being, which is evidenced by 2 indicators:
    - The engagement of the seeker-befriender-moderator interaction across the 4 time points—baseline (before the intervention), 3 weeks (conclusion of the intervention), and 6 and 9 weeks (carryover effect assessment)—that is indexed by the waiting period for seekers to receive a response. Delays are defined as a >48-hour waiting period and will be categorized based on the following reasons: (1) technical factors (eg, the befriender is not able to log into the platform to respond in time) and (2) human factors (eg, the befriender drops out from the study, and no replacement is found in time). An acceptable response time is within 48 hours, and this is emphasized during Acceset digital peer support training for befrienders [37].
    - The use of technical features of the Acceset platform that is measured by the seeker dropout rate at each stage of engagement with the Acceset platform, the number of visits on the study registration website, the number of participants who registered with Acceset, the average number of letters exchanged, and the average number of emotion and functional adjustment stickers and motivation graphic interface formats used [37].
  - Research question 1c: is the Acceset text-based intervention (ie, the platform) feasible and acceptable (ie, safe and timely) as an ongoing mechanism of support that identifies individuals who are at an unacceptably high risk of mental health conditions?
  - Hypothesis 1c: digital peer support is feasible and acceptable in offering support for emerging adults' mental well-being by identifying individuals who are at an unacceptably high risk of mental health conditions related to depression and suicidality, which is measured before and during engagement based on 3 means—specifically, the Acceset algorithm detection of the content of the letters, the moderators' vetting of the content of seekers' letters, and the seekers' self-report responses to the 9-item Patient Health Questionnaire [38] (refer to the Implementation Outcomes section for details [37]).
- Aim 2: the second aim is to elucidate whether Acceset digital peer support harnesses the 4 components of emerging adult mental health—mattering, selfhood, compassion, and mindfulness.
  - Research question 2a: does Acceset digital peer support enhance the 4 components among seekers and befrienders?
  - Hypothesis 2a: Acceset digital peer support (training) increases the 4 components among befrienders (before and after training) and seekers (over the course of the study across 4 time points).
  - Research question 2b: is Acceset digital peer support effective in improving emerging adult mental well-being?
  - Hypothesis 2b: digital peer support leads to significantly better mental well-being of seekers compared with the control group. This effect is sustained beyond the period of the intervention.
- Aim 3: the third aim is to investigate the mechanism of change in emerging adult mental well-being involving digital peer support (delivered by the Acceset platform).
  - Research question 3: what is the mechanism explaining the change in emerging adult mental well-being involving digital peer support?
  - Hypothesis 3: the initial level and rate of change (ie, growth factors) of befrienders' web-based support positively predict the growth factors of seekers' psychological well-being in accordance with latent growth curve modeling.

Methods

Trial Design

This trial is registered with the US National Library of Medicine ClinicalTrials.gov (NCT05083676). We are initiating an interventional prospective study with a hybrid design that evaluates both the implementation of the Acceset intervention (eg, fidelity, adoption, and utility) and participant outcomes (eg, anxiety and depressive symptoms) via a randomized controlled trial (RCT). The intervention comprises 2 components—digital peer support training and a digital text-based intervention (ie, the platform)—involving 3 features: digital markers of psychological well-being, the peer emotional disclosure process, and community engagement.

Participants and Study Setting

We plan to recruit 130 participants (100 seekers and 30 befrienders) at the National University of Singapore (NUS) to engage with the Acceset intervention in accordance with an Institutional Review Board–approved protocol. Participants will be recruited via the Research Participation program within the Department of Psychology at NUS, where students will be

awarded credits as part of the introductory courses for psychology. During recruitment, inclusion and exclusion criteria screening will be conducted via self-reporting. Participants qualified for inclusion (seekers) will be randomized into 2 arms. The seekers (n=50), befrienders (n=30), and moderators (n=30) in arm 1 will use Acceset for 3 weeks. The control group (n=50) in arm 2 will be wait-listed for Acceset use. It should be noted that the wait-listing approach is a standardized approach for RCTs pertaining to digital mental health [37,39,40].

We will recruit age- and gender-matched individuals from NUS. The 4–time-point questionnaire battery of arm 1 will be used to compare the mental well-being and help-seeking behavior with those in arm 2 [37]. Moderators will be recruited from the Singapore Executive Counselling and Training Academy. If an unacceptably high risk of depression and suicidality is detected at any time point by the moderator, who is a certified counselor, they will reach out to the participant, who will be directed to different clinical mental health support providers, including counseling centers and hotlines, on the NUS campus. On the basis of power analysis and the finding that 20% to 40% of the emerging adults enrolled in an IHL typically experience distress, this sample will provide a sufficiently powered comparator group.

Upon recruitment, seekers will be able to register in two ways: (1) by engaging with a Telegram chat channel, an instant messaging app that allows users to send text messages, photos, videos, stickers, and files, which is a prevalent mode of communication among young people, and (2) through the Acceset website. The user will provide their email address, password, age, and gender. When using Telegram, the seekers will submit consent to the privacy policy and terms of use and acknowledgment that they fulfill the criteria for research participation (being aged 19-25 years and having no clinically diagnosed mental illnesses). During the intervention, seekers will be able to anonymously share their emotional experiences by writing e-letters. In response, they will receive support from a peer (befriender) who has received Acceset digital peer support training. When using the Acceset website, an automated bot will function as a courier to deliver the letter to the Acceset platform. The chatbot will also inform the user when they have a letter in the mailbox. The user will log in to retrieve the response letter from their mailbox.

The letter exchange will be monitored by moderators—certified counselors with the required background and assessment tools to identify seekers at risk of depression and suicidality. These moderators have received certified trainings that are accredited by the Australian, New Zealand, and Asian Creative Arts Therapies Association and Swinburne University of Technology in Professional Counselling; have a master's degree in Social Science; and are certified by the Ministry of Education, Singapore, and the Executive Counselling and Training Academy to provide holistic counseling for students and supervision for counselors. Professionally, these moderators are experienced counselors at various IHLs; serve as vice-presidents of the Singapore Association for Counselling; and partner with schools and the Health Promotion Board, Singapore, to provide a range of counseling services to emerging and working adults.

The moderation protocol at the participant recruitment stage entails the screening of seekers using a validated psychological scale—the 9-item Patient Health Questionnaire (PHQ-9)—to exclude individuals at high risk of depression and suicidality. During the intervention phase, befrienders are also trained to alert moderators when seekers are at an unacceptably high risk of depression and suicidality, and the moderator vets all the letter exchanges between the seekers and befrienders for content of high negativity and suicidal thoughts and expressions. This moderation protocol aims to identify seekers who are at an unacceptably high risk of depression and suicidality and refer them to an appropriate mental health care provider, including counseling centers and hotlines, on the NUS campus.

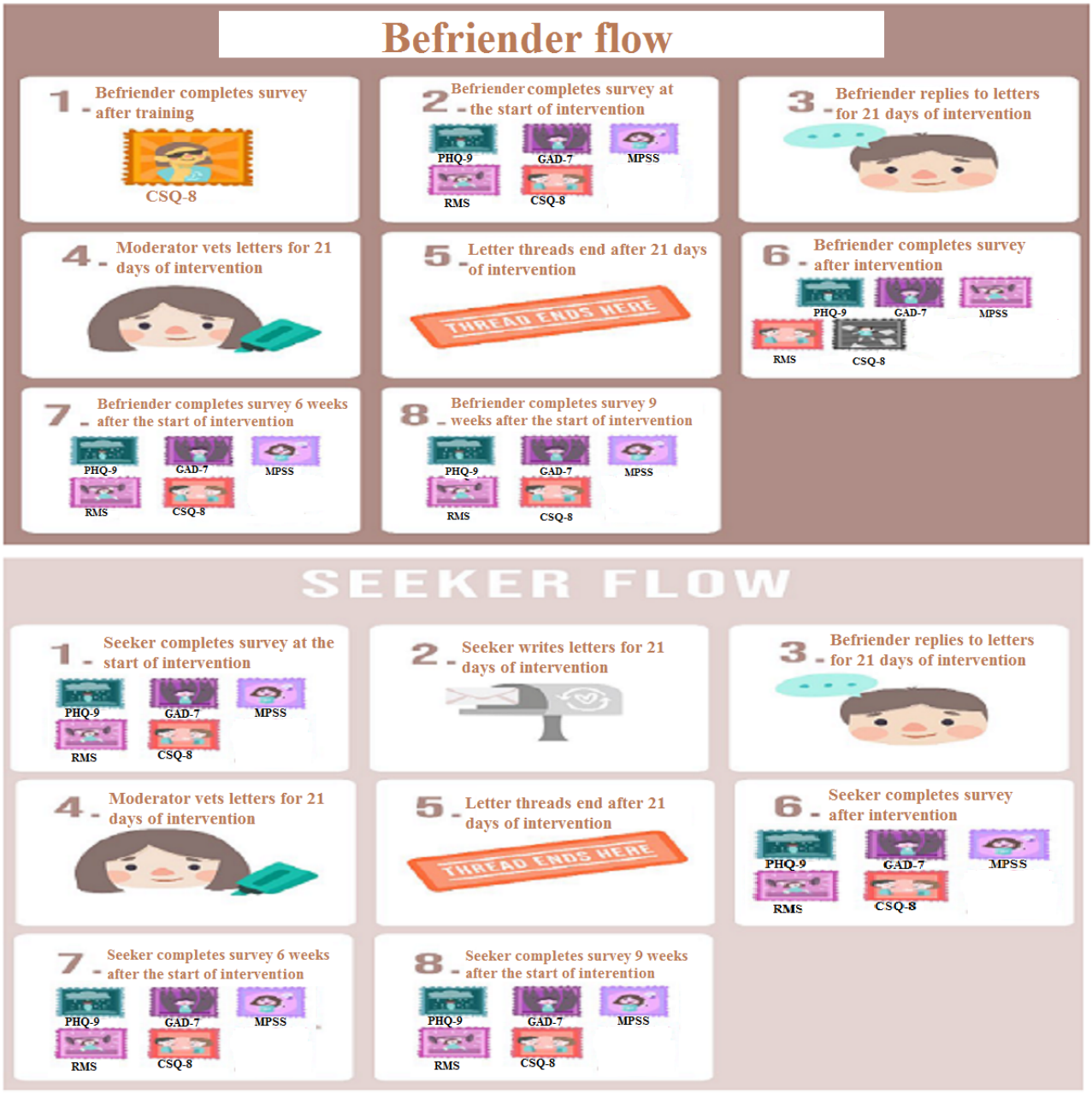
Each befriender will provide support to 3 seekers, receive notification from the Acceset platform on incoming letters, and work in partnership with the moderators to address the seekers' issues during the 3 weeks of letter exchange. Befrienders have the choice to discontinue the letter exchange with seekers if they feel discomfort having to address issues that they find challenging by informing trained moderators. Given the sensitive nature of the letter content, there may be issues that befrienders will be exposed to that they are not fully comfortable with and may cause distress. Therefore, it is a deliberate design to ensure that the befrienders are not left on their own in handling cases and that they work in partnership with the 2 trained and certified moderators to address the seekers' issues. The first point of contact for the befriender will be the 2 trained and certified moderators. In such cases, the befriender's workload decreases to 2 seekers.

The system will inform the seeker and obtain their consent to continue the conversation with a new befriender or end the letter thread. If the seeker chooses to continue, the system will notify all befrienders of the availability of an ongoing case, and interested befrienders can take it up. In addition, other trained befrienders (whom Acceset has trained beyond the recruited 30 befrienders for this study) will be activated to take up the case if no existing befrienders take it up. Similarly, when befrienders drop out of the study during the 3 weeks of letter exchanges, they will be replaced with other trained befrienders. Befrienders', seekers', and moderators' use of the Acceset platform is to remain completely anonymous such that the 3 parties do not have direct contact with one another, and seekers do not have discretion to switch befrienders on their own. In the event of disagreement between seekers and befrienders (eg, seekers are concerned with how their issues are not adequately addressed during the letter exchange), they will be able to notify the study team. The system will inform the seeker and obtain their consent to continue the conversation with a new befriender or end the letter thread. If the seeker chooses to continue, the system will notify all befrienders of the availability of an ongoing case, and interested befrienders can take it up. However, it should be noted that such situations will be rare given that moderators will vet all letter exchanges and work in partnership with befrienders to ensure that their responses are satisfactory. If seekers drop out of the study, their befrienders will continue with the reduced workload.

Befriender engagement will be monitored, and they will receive a reminder email after 48 hours if there is no reply to the seeker.

A questionnaire battery over 4 time points will be used to monitor befrienders and seekers (Multimedia Appendix 3). These time points will include baseline (before the intervention), 3 weeks (end of the intervention), and 6 and 9 weeks (carryover effect measurement; Figure 1) [37]. Signals for closure will be done through an email reminder sent 7 days before the conversation ends, and another email will be sent to inform seekers and befrienders when the thread officially closes after 21 days. Where there are issues that reflect high negativity and suicidal thoughts and expressions at any point in the letter thread, we will immediately link the seekers to the appropriate professional counseling resource.

Figure 1. Diagrammatic flow in terms of sequence of events on the Acceset digital text-based intervention (ie, the platform). CSQ-8: Client Satisfaction Questionnaire-8; GAD-7: Generalized Anxiety Disorder-7; MPSS: Multidimensional Scale of Perceived Social Support; PHQ-9: 9-item Patient Health Questionnaire; RMS: Rosenberg Mattering Scale.



Ethics Approval

This study will be performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the NUS (protocol S-20-144). Informed consent will be obtained from all individual participants included in the study.

Eligibility Criteria

The seeker inclusion criteria are as follows: emerging adults aged 19 to 25 years who are distressed but healthy—specifically, these individuals should exhibit some symptoms but have not been formally diagnosed with depression, anxiety, or a mental health disorder. The exclusion criteria (seekers) will include emerging adults who, during screening, are deemed to be at a high risk of suicide using a validated and standardized

psychological scale (PHQ-9) [37,38]. On the basis of empirical studies, the proposed cutoff is PHQ-9 >9, which has a sensitivity of 88% and specificity of 88% for major depression [37]. Above a score of 9, seekers will not be recruited for the study, and they will be referred or directed to different clinical mental health support providers, including counseling centers and hotlines, on the NUS campus.

The rationale for including individuals who do not meet the criteria for depression is that the Acceset intervention focuses on befrienders as peer supporters to seekers, and these befrienders are not certified and accredited counselors, unlike moderators. Importantly, it is not the responsibility of the befriender to serve as an advisor, solve the seekers' problems, or provide diagnoses of potential mental health issues. Inclusion of individuals who meet the criteria for depression would require support from professional counselors who have formal trainings and certifications. However, Acceset as an intervention platform is designed primarily for a healthy population of young people without formal diagnoses of mental health conditions to provide peer support.

The inclusion eligibility criteria also apply to befrienders, with an additional criterion of being aged ≥21 years. Seeker exclusion criteria apply to both befrienders and moderators. Moderator inclusion criteria are as follows: adults aged ≥21 years with certified trainings and accreditations (ie, at least a master's degree in social sciences or Counseling that is recognized by the Ministry of Education, Singapore, and the Executive Counselling and Training Academy) and professional experiences in providing counseling services to emerging adults. The exclusion criteria apply to both seekers and befrienders.

The Intervention

The Acceset intervention for this preliminary study comprises (1) training for befrienders to apply mattering, selfhood, compassion, and mindfulness to provide effective digital peer support (refer to the digital peer support training curriculum in Multimedia Appendix 4) and (2) a text-based intervention with Acceset incorporating digital markers that assess the following outputs: psychological well-being and the degree of community engagement as well as peer emotional disclosure [37].

Digital Peer Support Training

The core objective of Acceset is to enable peer befrienders to effectively support peer seekers. Befrienders will receive 4 hours of web-based training conducted by a licensed clinical or educational psychologist. This training consists of 1 hour of instructional content that enhances the befriender's knowledge of mattering, selfhood, compassion, and mindfulness and 2 hours of workshop training on the practical skills of applying these components to provide effective peer support.

Selfhood refers to self-knowledge (an awareness of one's strengths and unique qualities) [41]. The second type of selfhood is the interpersonal self (how the self evolves based on our interactions and relationships with others). The interpersonal self creates and sustains relationships and fulfills important roles to keep a favored position in the social system. The third type of selfhood refers to the self as an agent (having agency, control, and persistence in achieving a goal despite failure, frustration, and discouragement). Mattering, which refers to the extent to which we are important to the world and people around us [42], consists of three components: (1) importance (the interest and concern others bestow on us), (2) attention (from others; the extent to which people are aware of our presence and unique qualities), and (3) reliance (the degree to which others turn to us and make us feel that we are needed).

Compassion comprises 3 theoretical orientations—having compassion for others, receiving compassion from others, and having self-compassion—in reducing psychological distress and symptomologies [43], and there are 3 stages of developing compassion based on the well-established Compassion Cultivation Training with evidence from accumulating RCTs [44]. In the first stage, individuals become aware of their distress and develop self-compassion; in the second stage, they develop affective concern; and, in the third stage, they gain personal insights into the wish and readiness to relieve one's distress [44]. Mindfulness will be regarded as a flexible cognitive state in which individuals are actively present and notice novel aspects in both the environment and one's perspectives [45].

The proficiency of befrienders in applying these digital support skills will be evaluated through simulation and homework activities in which they will apply these skills to simulated letters that are adapted from actual cases of peer seeker emotional disclosure on the Acceset platform. All assignments will be reviewed and given feedback on. At the end of the training, befrienders are expected to apply the 4 components to their assigned peers' disclosed emotional experiences. All participants who complete the training will receive a training certificate and will be invited to take on live cases and be part of the study.

Acceset Text-Based Intervention (the Platform)

Acceset aims to serve as an intervention to strengthen emerging adult mental well-being via 3 means—assessing their psychological well-being with 3 digital features: emotionality, motivations, and functional adjustment. These features are intended to support users with a peer emotional disclosure process while also engaging an interconnected and accessible Singapore ecosystem and community as the basis of the support system.

Digital Features

Participants' emotionality, as reflecting their mental well-being, is assessed by their use of emotion stamps—a digital feature of the Acceset platform to measure negativity and positivity that is based on the Positive and Negative Affect Scale [46]. A total of 9 motivation graphic interface formats (GIFs)—dynamic images with corresponding captions—function to express a seeker's motivation to engage with the Acceset platform. There are 3 innate psychological motivations [34]. These include competence (to exert control, cope with specific problems, and make changes to one's behavior and environment), autonomy (to act from choice), and relatedness (the need to belong and connect with others). Acceset also has a set of functional adjustment stickers as indicators of internalized and externalized problems. Internalized problems refer to those directed inward—toward the self—and often manifest as "tension, unease, and distress" [47]. When these internalized symptoms

compound, individuals may experience depression, anxiety, social isolation, and other challenges. On the contrary, externalizing problems are directed externally [48]. Individuals often disregard social norms and engage in conflicts and behaviors that cause discomfort to other people. When these externalizing problems are grouped together, they can potentially manifest as aggression, rule breaking, delinquency, and other behaviors.

Peer Emotional Disclosure

The Acceset text-based disclosure process collectively leverages technology and community engagement to form a web-based safety net for the development of a platform function that drives sustainable user engagement. This process begins when seekers engage with the Acceset platform to seek support with managing their emotional experiences. Before writing their first letter, seekers will select the social contexts of the issue. These may include friends, finances, family, work, and school. On the basis of the disclosed emotional experiences, the information presented will pertain to where the issues arise, with whom the issues occur, and which issues adversely affect mental well-being. During the course of the letter exchange, seekers will express their negativity and positivity through the emotion stamps, indicate their psychological needs using the motivation GIFs, and describe the effects of the emotional experiences through the function adjustment stamps.

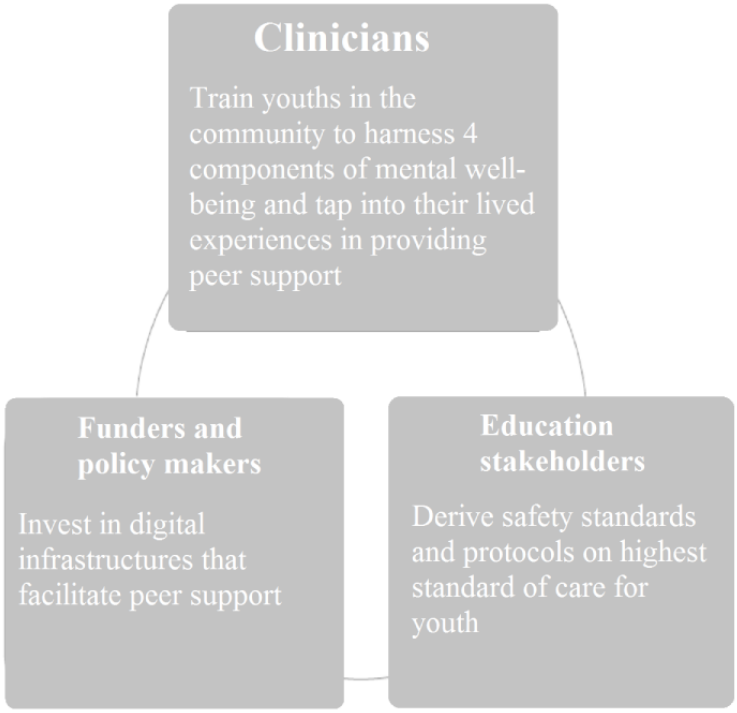
The seeker-befriender interaction dynamic is facilitated digitally, with no in-person visits or interactions. Before and during the letter-writing process, a pop-up message reminds both befrienders and seekers that the use of the Acceset platform is to remain completely anonymous and that personal information may not be revealed in any way. In matching befrienders and seekers, 3 factors are considered: the timing when seekers reach out, the availability of befrienders, and befrienders' knowledge of the nature of the seekers' emotional experiences. Some befrienders may have more in-depth knowledge of certain issues based on their lived experiences and will prefer to support seekers on those issues. Thus, when the seekers write a letter, the social context of the letter is made known to the befriender, who will then select their preferred seeker based on their ability to relate and respond. The approach of matching befrienders and seekers is intended to facilitate effective peer support intervention [29]. Through the digital peer support training and the guidance of the moderators—certified counselors who will vet the e-letter drafts from the befrienders—the befriender's role is to provide support by enhancing a sense of mattering, strengthening selfhood, exploring compassion, and cultivating mindfulness among seekers. Importantly, it is not the responsibility of the befriender to serve as an advisor, solve the seekers' problems, or provide diagnoses of potential mental health issues.

Community Engagement

The essence of the Acceset intervention draws on emerging adult support within the Singapore ecosystem and community by tapping into the shared experiences among emerging adults and training them to harness the 4 components of psychological well-being to bolster each other's mental well-being (Figure 2). Seekers can further the community efforts by joining as befrienders and being trained to provide web-based peer support. By engaging clinicians, psychologists, and counselors, the Acceset intervention emphasizes the availability of peer support that leverages the lived experiences of the community. The building of the seeker-befriender-moderator relationship also aims to deepen the authenticity of peer support rather than being a "transaction" for referral, as evidenced by the effective implementation of the intervention when seekers' and befrienders' satisfaction with the support system and sense of perceived social support relate positively to their psychological well-being.

In addition to a community-based structure for facilitating digital peer support, Acceset engages education stakeholders at various IHLs in the advice of safety standards and protocols for effective and compliant digital peer support that is in accordance with the ethics of members of the helping profession. Education stakeholders play an important role in normalizing a new service delivery model through various formal and informal outreach channels. This could entail mass mailing of a new service and organization of an information session where students can learn more about the new service and how participating in it can be beneficial for their mental well-being. Attending college can be a particularly stressful time, especially in Asian societies with a high cultural value ascribed to educational achievement and a high level of competition [49,50]. The experience of heightened psychological distress is a salient problem, with an average of 20% to 40% of students reporting distressed symptoms [50]. This finding, coupled with the increasing number of emerging adults enrolled in 2- or 4-year colleges (40% in 2013 to 70% in 2018) [51], provides the impetus for leveraging a community approach in the development of digital peer support that intervenes in emerging adults' psychological well-being.

Figure 2. The Acceset intervention draws on digital peer support within the Singapore ecosystem and community.



Implementation and Clinical Study Outcomes

All implementation and clinical outcomes will be measured via the engagement with Acceset over 4 time points using the aforementioned questionnaire battery [37]. In this section, we delineate the outcome measures that correspond to each hypothesis examined in this study.

Implementation Outcomes

For research question 1a and hypothesis 1a, we will determine whether Acceset digital peer support training is an effective curriculum for befrienders in providing effective peer support. We will assess the adoption of and fidelity to the training curriculum through the letter exchanges between seekers and befrienders. The text of the letter exchanges will be evaluated in terms of the extent to which befrienders display fidelity in applying the 4 components of psychological well-being in response to seekers' disclosure. All correspondence will be anonymized before analysis, and the seekers' letters will only be used to provide content for the befrienders' responses. With respect to research question 1b, hypothesis 1b, research question 1c, and hypothesis 1c, we will evaluate the feasibility and acceptability of sustaining access to web-based peer support in terms of (1) initial and sustained engagement of seekers, befrienders, and moderators (ie, certified counselors); (2) the use of technical features of the Acceset platform; and (3) the identification of participants with high risk of mental health conditions relating to depression and suicidality.

This study will assess the waiting period for a seeker to receive a response. Delays (defined as a >48-hour waiting period) will be categorized based on the following reasons: (1) technical factors (eg, the befriender is not able to log into the platform to respond in time) and (2) human factors (eg, the befriender drops out from the study, and no replacement is found in time). An acceptable response time is within 48 hours, and this is emphasized during Acceset digital peer support training for befrienders. The seeker dropout rate at each stage of engagement with the Acceset platform will be assessed based on (1) the number of visits to the study registration website, (2) the number of participants who registered with Acceset, (3) the average number of letters exchanged, and (4) the average number of emotion and functional adjustment stickers and motivation GIFs used.

With regard to user referral to appropriate mental health support providers, the seeker-befriender-moderator interaction will identify participants at an unacceptably high risk of depression and suicidality before and during engagement based on 3 means. First, the Acceset algorithm will scan the content of the letter exchanges for high negativity and suicidal thoughts and expressions. Second, moderators with the required background and assessment tools will identify seekers at risk by vetting all the letter exchanges for high negativity and suicidal thoughts and expressions. Third, seekers will self-report their responses to the PHQ-9, and those that meet the clinical cutoff scores (PHQ-9 >9) will be excluded at the start of the study. During the course of the study across the 4 time points, seekers with an unacceptably high risk of depression and suicidality (PHQ-9 >9) will be referred to an appropriate mental health care provider, including counseling centers and hotlines, on the NUS campus. Seekers' self-reported responses to the PHQ-9 serve as the primary risk assessment to make referrals to appropriate mental health support providers.

At recruitment, we will assess the percentage of participants identified as being at an unacceptably high risk of depression and suicidality meeting the clinical cutoff of PHQ-9 >9 that has a sensitivity of 88% and specificity of 88% for major depression [38] and exclude them from the study. During the course of the study, we will ascertain the percentage of events when a

befriender correctly alerts the moderator that the seeker is at an unacceptably high risk of depression and suicidality as confirmed by the moderator, who will vet every letter exchange. During the course of the study and for every letter exchange, we will tabulate the percentage of events when a moderator correctly identifies a seeker with an unacceptably high risk of depression and suicidality. Both the befrienders and moderators will use the PHQ-9 as a systematized coding structure to code seekers' letter content to ensure generalizability and validity in risk assessment across both coders—befrienders and moderators. Finally, we will tabulate the percentage of events when a seeker who is at an unacceptably high risk of depression and suicidality (both during the recruitment process and during engagement with the platform) receives directions to an appropriate mental health care provider, including counseling centers and hotlines, on the NUS campus.

The study team will alert the counseling center on the NUS campus about the referrals of at-risk seekers to ensure that adequate and appropriate support is provided to them. In addition, at weeks 6 and 9, there will be a follow-up on all seekers (to measure carryover effects), which helps ensure the psychological safety of the seekers. At the start of the study, all seekers are provided with the participant informed consent and information sheet, which states that they will be referred to and their information shared with the NUS counseling center if their risk assessment across the 4 time points indicates an unacceptably high risk of depression and suicidality (PHQ-9 >9).

Clinical Outcomes

To address research question 2a and hypothesis 2a, we will examine whether the Acceset training curriculum can enhance the 4 components of psychological well-being among befrienders and seekers. We will compare the change in mattering, selfhood, compassion, and mindfulness scores of befrienders between baseline and following Acceset training (ie, before vs after training) and those of seekers over the course of the study. As for research question 2b and hypothesis 2b, we hypothesized that engagement with Acceset digital peer support will lead to improved mental well-being of the seekers compared with the control group and that this effect may be sustained beyond the period of the intervention. To assess these effects, we will evaluate the change in mental well-being of the participants in both study groups (intervention and control) after 3, 6, and 9 weeks from baseline using self-report questionnaires. Seekers will provide responses pertaining to help-seeking behavior beyond the Acceset platform at weeks 6 and 9 using the perceived social support measure in the questionnaire battery. We will assess the correlations of the 3 digital features—comprising emotion and functional adjustment stickers and motivation GIFs, which reflect seekers' mental well-being during engagement with the platform—with their well-being scores from the questionnaires.

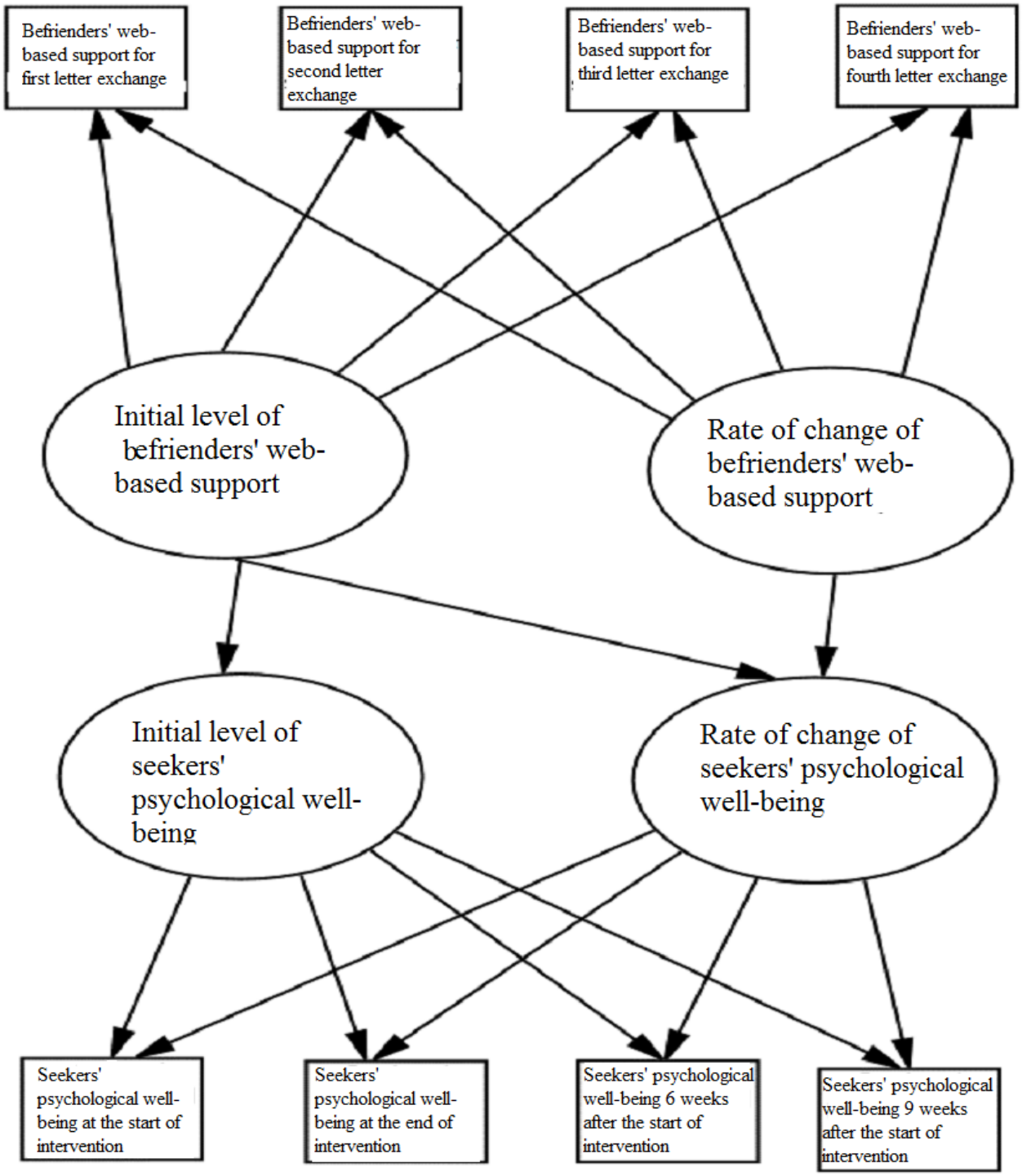
The scale or set of scales used to assess the clinical outcomes, including the 4 components of psychological well-being underpinning the Acceset training curriculum, measures of seekers' well-being, and perceived social support, are outlined in the following paragraph.

"Mattering" will be assessed via the Rosenberg Mattering Scale [52]. *Selfhood* comprises self-knowledge, interpersonal self, and self-agency and will be assessed via the following respective scales: the Rosenberg Global Self-Esteem Scale [53], the Self-Consciousness Scale [54], and the General Self-Efficacy and Social Self-Efficacy Scales [55]. *Compassion* will be assessed as operationalized in the Compassion Cultivation Training [56] comprising three stages: (1) an awareness of distress, (2) affective concern, and (3) a responsiveness or readiness to help relieve that distress (motivational). *Mindfulness* will be regarded as a flexible cognitive state in which individuals are actively present and notice novel aspects in both the environment and one's perspectives [45]. We will evaluate the participants' responses based on the degree to which they harness the approaches pertaining to the enhancement of mindful self-acceptance: (1) identifying novel aspects of the situation or perspective; (2) demonstrating "work in progress" by using possibility words such as "could be" and offering other interpretations of the situation their peers have shared; (3) highlighting puzzles and paradoxes in the peer-disclosed emotional experiences (eg, how their peers may feel victimized yet are responsible for being in that situation), which builds tolerance for ambiguity and decreases the experience of psychological symptoms; (4) noticing humorous aspects of the situation; (5) perceiving the situation from multiple perspectives; (6) considering alternative (useful) aspects of a problematic context or the silver lining; (7) emphasizing a mental file of positive memories; and (8) encouraging peers in mindfulness journaling. *Anxiety* will be measured using the Generalized Anxiety Disorder Questionnaire [57]. *Depression* will be measured using the PHQ-9 [38]. *Perceived social support* will be assessed using the Multidimensional Scale of Perceived Social Support [58].

Mechanism of Action

For research question 3 and hypothesis 3, we will elucidate the mechanism of change that links digital peer support intervention to emerging adult mental well-being (Figure 3). Specifically, we will assess whether and how the level at the start of the study and the rates of change from baseline to weeks 3, 6, and 9 in befrienders' support relate to seekers' mental well-being.

Figure 3. A mechanism of change linking befrienders' web-based support and seekers' psychological well-being.



Data Collection, Management, and Analyses

Acceset will serve as the data collection platform. Participants (both seekers and befrienders) will initially enter their details on the sign-up page, which includes role preference (seeker, befriender, or either), email, date of birth, gender, nationality, ethnicity, monthly household income, and password. The user will be required to answer the PHQ-9 to determine their eligibility. An email will also be sent to the users' registered email address for verification. Once eligible individuals are selected and assigned their respective roles, they will be given a unique nonidentifying ID to participate in the study. Participants' self-reported questionnaire responses at each time point and the digital letter exchange content will be securely stored and tied to their specific IDs. The data collected will be stored on the cloud servers of the leading author's affiliated institution. Once the research concludes, the information will be downloaded to a Microsoft Excel sheet, and all personal information will be deidentified for data analyses.

A power analysis assessed the adequate sample size needed for the RCT to have sufficient power to detect valid effects. The

intervention (n=50) and control (n=50) arms were derived from multiple dependent variables assessing implementation testing (ie, feasibility and utility) and clinical outcomes. To address any potential challenges with missing data, the Little Missing Completely at Random Test will address potential missing data via full information maximum likelihood imputation [37,59]. Maximum likelihood estimation is a method that ascertains the parameter values of a model using the mean and variance and maximizes the chance that the values generated are closest to those observed.

The following approaches will be used for data analysis and interpretation. Independent-sample 2-tailed *t* tests will compare the intervention and control groups. Bonferroni post hoc tests will control for multiple comparisons. For both the intervention and control groups, additional independent *t* tests will compare seekers who provided data across all 4 time points with those who dropped out from the study for different reasons to ascertain if the sample with data across all 4 time points and the sample with fewer data points bias our results. For instance, seekers may drop out when risk assessments identify them as having a high risk of depression and suicidality during the course of the study. There will also be instances when befrienders discontinue the letter writing because of the sensitive nature of the letter content that may cause distress and befrienders not being fully comfortable, and the system will inform the seekers and obtain their consent to end the letter thread instead of continuing the conversation with a new befriender. Second, each participant's emotional experiences disclosed on Acceset will be extracted based on the definitions of the 4 components of psychological well-being. Latent Dirichlet allocation analyses in R (R Foundation for Statistical Computing) and content analysis will be used [37,60,61].

Latent growth curve modeling (LCM) will investigate the mechanism of change involving the trajectories of peer support in predicting the change in psychological well-being [59]. LCM delineates whether and how the exposure to the intervention changes over time with psychological outcomes by estimating and comparing different baseline latent growth models, including linear, quadratic, and nonlinear curve fitting (ie, optimal fit). In other words, LCM elucidates whether the trend in befrienders' peer support predicts the trend in seekers' psychological well-being (Figure 3). Current research assessing peer support intervention for the mental health of young people does not consider the mechanism of change. By establishing a change model, this protocol provides a basis for building the therapeutic potential of digital peer support that harnesses the components of emerging adult mental well-being to reduce psychological symptoms. Specifically, LCM elucidates whether and how the intervention affects the development of psychological symptoms and how they unfold over time among emerging adults. This finding provides actionable knowledge for timely and relevant digital peer support.

Results

This protocol received approval from the Institutional Ethics Review Board of NUS in October 2021. Recruitment will commence in January 2022. Data collection began in March 2022 and was completed in June 2022. Data analysis started in July 2022 and is currently in progress. We aim to report the preliminary study outcomes in December 2022. The effect size will be analyzed using the Cohen *d* index with a significance level of .05 (95% reliability) and 80% power statistic [37]. A total of 100 seekers, 35 befrienders, and 2 moderators were recruited in January 2022.

Discussion

Principal Findings

This protocol delineates the design of an RCT to assess the implementation and clinical effectiveness of Acceset. To our knowledge, the proposed intervention is the first to incorporate and validate digital markers of psychological well-being, harness components of emerging adult mental well-being, and elucidate a mechanism of change involving digital peer support in mitigating emerging adults' psychological symptomologies. We hypothesized the following: (1) the digital peer support training will be effective for befrienders in providing peer support, as demonstrated by the adoption of and fidelity to the training curriculum with significantly higher scores after training than before training on the 4 components of well-being (selfhood, mattering, compassion, and mindfulness); (2) the digital peer support intervention will be feasible and acceptable in offering support for emerging adults' mental well-being through the engagement of seeker-befriender-moderator interaction over the Acceset platform throughout the course of the study (baseline [before the intervention], 3 weeks [the end of the intervention], and 6 and 9 weeks [to measure carryover effects]) and the use of the platform's technical features; (3) the digital peer support intervention will be feasible and acceptable in offering support for emerging adults' mental well-being by identifying individuals who are at an unacceptably high risk of mental health conditions related to depression and suicidality based on the Acceset algorithm, moderators' vetting of the letter exchanges, and seekers' self-report responses to the PHQ-9; (4) the digital peer support intervention will lead to significantly better mental well-being of seekers compared with the control group, with the effect sustained beyond the period of the intervention; and (5) the mechanism of change, as indexed by LCM, will reveal that the initial level and rate of change (ie, growth factors) of befrienders' web-based support positively predict the growth factors of seekers' psychological well-being.

If successful, this novel mHealth intervention will provide the parameters and conditions required to validate the effectiveness of digital peer support interventions in real-world settings for emerging adult mental well-being. This intervention may, in turn, represent a scalable, sustainable, and low-cost prevention strategy that has considerable potential to support positive psychological well-being among young people, especially in coping with the life-course implications of the global pandemic.

Strengths, Limitations, and Conclusions

The key strengths of the proposed intervention are the scalability and sustainability of both the Acceset digital peer support training and text-based intervention (ie, the platform). Existing evidence suggests that, for the scalability of web-based nonprofessional peer support training to attain the desired reach,

training should incur minimal cost and be available to individuals across geographical locations and from diverse backgrounds and abilities [22,62]. Consistent with these findings, the digital peer support training is designed to maximize reach and is widely accessible at scale. A benefit of using a web-based format for the 3 hours of training is its link to existing IHL curricula that are comprised of 1 hour of lecture and 2 hours of tutorial discussion. This format may enable IHLs to serve as key delivery partners in rolling out the training program on the web for diverse student populations and across physical locales. Importantly, existing findings suggest that digital mental health interventions that harness peer support and adopt dual community engagement approaches (active and consultative) drive optimal user engagement [28]. The Acceset intervention uses the active method of community engagement to provide web-based safety support for young people. This form of peer support is affordable and readily available as it draws on the common lived experiences of the community, with peers functioning as befrienders and moderators who are licensed mental health professionals or counselors to provide their fellow peer seekers with emotional support. By using the community consultative method, college students aged 19 to 25 years from IHLs in Singapore were consulted in co-designing the Acceset platform.

Results from a systematic review and meta-analysis of RCTs on the sustainable effects of mental health interventions for students from IHLs emphasize the significance of a multisystemic approach [63-65]. This approach entails the contributions from the individual, community, and societal levels to maximize the effectiveness and sustainability of psychological interventions for mental health, especially for emerging adults [63-65]. The web-based peer emotional disclosure and support system of the Acceset intervention is envisioned to be self-sustainable as the seeker-befriender-moderator dynamic is characterized by individual contributions, with the opportunity for seekers to join the peer support network as befrienders to expand the web-based network. In addition, the Acceset intervention taps into the community and society levels by leveraging technology and engaging clinicians, psychologists, and counselors in the community to further the sustainability of digital peer support. At the macrosystemic level, Acceset serves as a platform for community-driven cocreation, validation, and potential deployment. Collaborations with policy makers and IHLs in designing safety standards and protocols for emerging adults engaged in digital peer support may bolster platform sustainability by normalizing a new service delivery model.

A possible limitation of this study is the use of self-reported measures for the clinical outcomes of this trial, which could be subject to under- or overestimation of psychological well-being scores. This approach is necessary because of confidentiality and feasibility considerations, especially with the anonymity of the digital letter exchange on the Acceset platform, and is consistent with the standard protocol of school-based trials for peer-led mHealth interventions for young people [62]. To reduce self-report bias, whenever seekers and befrienders log in to the Acceset text-based platform both before and for the duration of the study, pop-up messages function to remind them of strict anonymity, with no in-person interactions or sharing of personal information that will reveal their identities.

The results of this study on validating the digital markers of psychological well-being on the Acceset platform could potentially be used to triangulate evidence with self-report measures and biomarkers of psychological well-being. Future research may continue to accumulate evidence on these digital markers of psychological well-being and incorporate biomarkers such as cortisol levels and blood pressure to provide a different method of data collection to enhance the validity and reliability of clinical outcomes on the mental well-being of young people. The evidence that is built on a single-site superiority trial outlined in this protocol limits the external validity of digital peer support interventions in real-world settings [28]. Future research should consider properly powered and rigorous studies using multiple trials of strategies and multiple sites to build the evidence on the effects of digital interventions addressing emerging adult mental health. Notwithstanding these limitations, this study's development and validation of a novel digital innovation for emerging adult mental well-being may provide important contributions to the field of mental health [8,28].

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Authors' Contributions

GHY conceptualized and designed the study, obtained ethics approval and clinical trial registration, and drafted the manuscript. WC was responsible for advising the design of the digital peer support training curriculum. LNL is responsible for participant recruitment and follow-up. MO is in charge of data collection and management. DH was involved in advising the ethics approval and clinical trial registration and drafting the manuscript. All authors approved the manuscript.

Conflicts of Interest

MO is chief executive officer, founder, and shareholder of Acceset Pte Ltd. Acceset Pte Ltd was not a funder of this study. DH is a scientific founder and shareholder of KYAN Therapeutics, which is developing personalized medicine platforms. DH is also an inventor of current and pending patents pertaining to digital therapeutics and food technology.

Multimedia Appendix 1
Information on Acceset—a social enterprise that provides digital text-based peer support intervention for emerging adult mental well-being.
[PDF File (Adobe PDF File), 689 KB - resprot_v11i9e34602_app1.pdf]

Multimedia Appendix 2
Components extracted from consultations with emerging adults about their lived experiences of mental well-being.
[PDF File (Adobe PDF File), 108 KB - resprot_v11i9e34602_app2.pdf]

Multimedia Appendix 3
Questionnaire battery to assess the variables in the study.
[PDF File (Adobe PDF File), 152 KB - resprot_v11i9e34602_app3.pdf]

Multimedia Appendix 4
Digital peer support training curriculum.
[PDF File (Adobe PDF File), 453 KB - resprot_v11i9e34602_app4.pdf]

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Abbreviations

GIF: graphic interface format
IHL: institute of higher learning
LCM: latent growth curve modeling
mHealth: mobile health
NUS: National University of Singapore
PHQ-9: 9-item Patient Health Questionnaire
RCT: randomized controlled trial

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Protocol

Transcultural Adaptation of and Theoretical Validation Models for the Spanish Version of the Nurses' Global Assessment of Suicide Risk Scale: Protocol for a Multicenter Cross-sectional Study

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Abstract

Background: The use of validated instruments means providing health professionals with reliable and valid tools. The Nurses' Global Assessment of Suicide Risk (NGASR) scale has proven to be valid and reliable in supporting the nursing evaluation of suicide risk in different languages and cultural environments.

Objective: The aims of our study are to translate and adapt the NGASR scale for the Spanish population and evaluate its psychometric properties in patients with suicide risk factors.

Methods: The translation, adaptation, and modeling of the tool will be performed. The sample will include 165 participants. The psychometric analysis will include reliability and validity tests of the tool's internal structure. The tool's reliability will be assessed by exploring internal consistency and calculating the Cronbach α coefficient; significance values of .70 or higher will be accepted as indicators of good internal consistency. The underlying factor structure of the Spanish version of the NGASR scale will be assessed by performing an exploratory factor analysis. The Kaiser-Meyer-Olkin measure of sample adequacy and the Bartlett sphericity statistic will be calculated beforehand. For the latter, if *P* is <.05 for the null hypothesis of sphericity, the null hypothesis will be rejected.

Results: Participants will be recruited between April 2022 and December 2022. Our study is expected to conclude in the first quarter of 2023.

Conclusions: We hope to find the same firmness that colleagues have found in other countries in order to consolidate and promote the use of the NGASR tool in the Spanish population. The prevention and treatment of suicidal behavior require holistic, multidisciplinary, and comprehensive management.

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KEYWORDS

mental health; suicide; psychiatric nursing; Spanish; translate; translation; scale; measurement; assessment; adapt; adaptation; cultural; transcultural; suicidal; nurse; nursing; psychiatric; public health; prevention; treatment; risk; development; lethal; patient; scientific literature; variables; reliability; validate; validity; tool; Nurse´s Global Assessment of Suicide Risk; psychometric

Introduction

Nowadays, suicide is a public health issue for which prevention and treatment must be prioritized by macromanagement, mesomanagement, and micromanagement in health programs worldwide [1]. Suicidal behavior is determined by the complex interplay among factors that pose a risk for the development of lethal behavior, risk factors and predisposing circumstances that may determine and precipitate suicidal behavior, and protective factors that provide life-sustaining safety [2,3].

The World Health Organization estimates that almost 800,000 people commit suicide every year worldwide, and for each of these suicides, it is estimated that there are 20 suicide attempts [4]. Therefore, we can estimate that there are more than 16 million suicide attempts every year worldwide. Suicide attempts are repeated by 15% to 30% of patients within 1 year, and almost 2% end up committing suicide within 5 to 10 years of their initial suicide attempt [5]; suicide attempts are therefore the most relevant risk factor [6]. Internationally, the countries with the highest suicide rates are Lithuania, South Korea, and Slovenia, where the suicide rate exceeds 30 cases per 100,000 inhabitants. Greece, Turkey, and South Africa appear at the bottom of the list, with suicide rates of less than 4 deaths per 100,000 inhabitants [7]. In Spain, more than 3500 people commit suicide every year, and this has been on an upward trend since 2014, with the suicide rate exceeding 10 suicides per 100,000 inhabitants [8]. The highest suicide rates per inhabitant and per autonomous community are in Asturias, Galicia, and Murcia. Cantabria, Ceuta, and Melilla have the lowest rates. Both nationally and internationally, hanging and jumping from a height are the most commonly selected methods [7].

Risk assessment scales for suicidal behavior are instruments that are available to health care providers in clinical practice and research. These instruments guarantee that quality standards are met in the results of their measurements and allow for the systematizing and universalizing of perceived observations. In order to support health care professionals in systematizing and assessing suicidal risk, it is important to determine the most appropriate intervention, as well as how to record cases and the care provided, and use validated suicide risk assessment scales that always require prior consultations with the patients and clinical interviews [8,9]. Among the most commonly used scales are the Horowitz Suicide Risk Questionnaire [10], Beck Hopelessness Scale [11], Beck Scale for Suicide Ideation [12], Hamilton Depression Inventory [13], Plutchik Suicide Risk Scale [14], Reasons for Living Inventory [15], and the Nurses' Global Assessment of Suicide Risk (NGASR) scale [8]. In addition, after the validation of such scales for specific populations, they can be converted into a web-based format and further developed for use on a web-based platform that facilitates registration and evaluation for health care professionals [16,17].

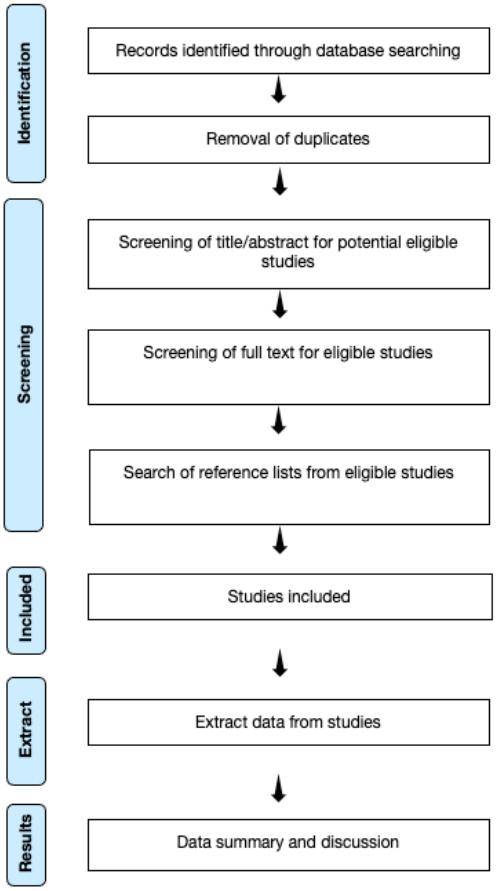
The NGSAR scale, which is noted for its ease of use [18], has been included as a suitable tool for assessing suicide risk in the Registered Nurses Association of Ontario's best practice manuals [19]. In Spain, nurses are the first line of care; therefore, having a scale with good psychometric properties in assessing suicide risk has become essential [20]. Taking into account the relevance and wide use of the NGASR in clinical practice and research and the fact that the scale has been validated in different languages (eg, German, Mandarin Chinese, Portuguese, Korean, and Italian) with good validity and reliability [8,18,21-29], the aims of this work are to translate and adapt this scale in Spanish—the second most spoken language in the world [30]—and evaluate its psychometric properties in patients with risk factors and suicidal behaviors.

Methods

Search Strategy

Initially, a review of the literature will be conducted in order to learn about previous adaptions in different languages and cultural environments and about the psychometric characteristics of the NGASR. A search for articles indexed in major health science databases will be performed. In addition, the bibliographic references of the included reviews will be searched. The results will be assessed for inclusion by 2 independent reviewers, and an assessment of methodological quality and data extraction will be performed. The search for scientific literature will be conducted based on the following keywords: *Suicide Attempted*, *Nurse*, *Risk Assessment*, *Risk*, *Scale*, and *NGASR*. They will be combined by means of Boolean operators ("AND" and "OR") and adapted to each database in a specific way. The literature review procedure that will be followed in our study is described in Figure 1.

Figure 1. Flowchart of the protocol.



Translation, Adaptation, and Modeling

Before testing its psychometric properties, the NGASR scale will be translated and culturally adapted from its original English version to Spanish. The NGASR scale was developed by Cutcliffe and Barker [8] in 2004 and consists of 15 items, of which each has a score of 1 or 3 points. Variables such as hopelessness, depressive symptoms, suicidal plans, the grief process, and a history of previous suicide attempts are scored with 3 points, while the rest of the variables are scored with 1 point. A final score of 0 to 5 points indicates low suicide risk, scores of 6 to 8 indicate intermediate suicide risk, scores of 9 to 11 indicate high suicide risk, and scores of ≥12 indicate a very high level of suicide risk. These items were designed so that during interviews, nursing staff can collect the necessary information for each of the variables (the scale is heteroadministered).

We will follow the guidelines published by Beaton et al [31], which divide the process into the following six steps: translation, synthesis, back-translation, back-translation synthesis, an expert review of the translated version, and pretesting.

For this purpose, a nursing professional expert in mental health and a bilingual nursing professional will each lead 1 of 2 independent groups that will carry out the translation and adaptation process for an initial Spanish version. As such, 2 initial Spanish versions will be developed (*Version 1–group A* and *Version 1–group B*). After comparing the two versions and in order to reach consensus on the discrepancies, the criteria of both groups will be unified, and a final version of the document will be created in Spanish (ie, the NGASR–Spanish version [NGASR-SPN]), which will be back-translated into English by an official entity that will certify this process. The back-translated version (the NGASR-SPN) will be provided to the original authors to confirm the accuracy of the instrument.

The NGASR-SPN will be evaluated by 10 mental health specialist nurses with more than 5 years of experience.

Participants in the Validation Process

A sample of 165 patients (10 patients for each item on the NGASR plus 10% to avoid possible losses) who are admitted to one of the units within La Rioja's mental health network. These units will comprise primary care mental health units, day hospitals, partial hospitalization units, short stay hospitalization units, medium stay hospitalization units, and long stay hospitalization units.

The inclusion criteria for participation in the study will be (1) people aged over 18 years; (2) patients diagnosed with a mental disorder according to the clinical descriptions and diagnostic guidelines of the *International Classification of Diseases, 11th Revision* [32] and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [33]; and (3) patients undergoing follow-up or treatment in one of the mental health departments of La Rioja Health Service.

The exclusion criteria will be (1) civilly incapacitated patients, (2) patients with cognitive or perceptual impairments, and (3) patients whose first language is not Spanish.

The sample size—165 patients—was estimated according to the criteria for a factor analysis with a minimum of 10 patients for each item on the NGASR [34], and another 10% will be recruited to avoid possible losses.

Data Analysis

The psychometric analyses of the Spanish version of the NGASR will include tests of the reliability and validity of its internal structure. The reliability of the scale will be assessed by exploring internal consistency and calculating the Cronbach α coefficient; significance values of .70 or higher will be accepted as indicators of good internal consistency [35].

The underlying factor structure of the NGASR-SPN scale will be assessed by performing an exploratory factor analysis. To assess the relevance of performing an exploratory factor analysis on the sample, the Kaiser-Meyer-Olkin measure of sample adequacy and the Bartlett sphericity statistic will be calculated beforehand. The adequacy of the sample for these analyses will be determined with optimal values for Kaiser-Meyer-Olkin measure, and in the case of the Barlett test of sphericity, if *P* is <.05 for the null hypothesis of sphericity, the null hypothesis will be rejected to ensure that the correlation matrix is adequate for obtaining a factor model that is able to properly describe the data.

The data will be coded and recorded in a computer format. Data processing and statistical calculations will be carried out with the SPSS Statistics software (IBM Corporation) [36].

Ethics Approval

To carry out the validation of the NGASR-SPN scale for the Spanish population, prior authorization has been requested from the Ethics Committee for Research on Medicines in La Rioja (reference number: PI-467). The patients will be informed of the objectives and methodology of the work, and we will request them to provide their free, voluntary, and informed consent. We will guarantee data confidentiality and use the information obtained exclusively for research purposes in accordance with *Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights* [37] and *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data* [38].

Dissemination

The results obtained in the process of adapting the NGASR to the Spanish population will be made available to regional health services and university centers at the national level by the Biomedical Research Center of La Rioja, the University of La Rioja, and Salamanca Biomedical Research Institute. The results will also be disseminated in congresses of psychiatry and nursing that recognize and are interested in the health impacts of our study, as well as scientific journals with national and international impacts. We will follow the phases described in Table 1.

Table 1. Study phases.

Phases and activities	2021			2022	
	October	November	December	January	February
Planning					
Contact the authors of the instrument	✓				
Review the theoretical framework and search for bibliographical references	✓	✓			
Analysis of the validation process developed in other countries		✓			
Preparation of an informed consent document for patients	✓				
Drafting of a document for the research ethics committee	✓				
Elaboration of research protocol and acceptance by the authors	✓	✓			
Research ethics committee authorization		✓			
Implementation					
Briefing of experts on the translation process of the tool	✓				
Comparison of the versions translated by both groups of experts and consensus		✓			
Back-translation of the final version by a certified body		✓			
Contact the authors to show them the translated version		✓			
Briefing meeting with the nursing professionals who will evaluate the first translated version in practice		✓			
Compilation of the study sample		✓	✓	✓	
Statistical analysis				✓	
Interpretation of the results obtained				✓	✓
Organization of the data obtained				✓	✓
Elaboration of the discussion and conclusion				✓	✓
Presentation to the authors of the draft and review of contributions					✓
Selection of the most appropriate journal for dissemination					✓
Dissemination					
Submission of the work to a journal of scientific interest					✓
Organization of a conference to present the results to the health network					✓
Presentation of the validation process at a national or international congress of scientific interest					✓
Working meeting on the process: aspects for improvement, strengths, weaknesses, and opportunities					✓

Results

Participants will be recruited between April 2022 and December 2022. Our study is expected to conclude in the first quarter of 2023.

Discussion

We believe that the results of our study can help prevent and manage suicidal behavior in the population, since the use of validated instruments means providing health professionals with reliable and valid tools. Several studies have demonstrated the robust properties of the NGASR scale in different languages and cultural environments. However, no study has validated the NGASR in Spanish—one of the most widely spoken languages in the world [30]. With our study, we hope to find the same firmness that colleagues have found in other countries in order to consolidate and promote the use of this assessment tool in the Spanish population. The scale must first be culturally adapted to the environment where it will be used, and then its psychometric characteristics must be remeasured [39].

Validating this scale in Spanish will provide a standardized suicide risk assessment instrument that can be used by nursing staff, be recorded in patients' electronic medical records, and facilitate assistance and further research studies for preventive purposes. As the NGASR-SPN will be made available to health care providers in the first line of care, such as nurses, the scale will be a key tool in the work of any nurse in the Spanish population. Furthermore, a clear benefit of the validation of specific instruments in the field of health for a circumscribed context is the ability to compare the results obtained with those of studies that are carried out in other countries and use the same

instrument. Such validation favors the universality of care, and the NGASR-SPN will result in less variability in nursing practices [40,41].

The magnitude of suicide is a serious public health problem; therefore, it is necessary to develop validated tools for its evaluation, with the ultimate goal of reducing the prevalence of suicidal behaviors.

The translation of the NGASR scale into Spanish will allow nurses to perform a more accurate assessment of suicide risk in Spanish-speaking countries, thus contributing to the provision of interventions aiming to prevent suicidal behaviors.

Conflicts of Interest

None declared.

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Abbreviations

NGASR: Nurses' Global Assessment of Suicide Risk

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Protocol

Assessing Cognitive Behavioral Therapy for Insomnia to Improve Sleep Outcomes in Individuals With a Concussion: Protocol for a Delayed Randomized Controlled Trial

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Abstract

Background: Sleep disturbances post concussion have been associated with more frequent and severe concussion symptoms and may contribute to poorer recovery. Cognitive behavioral therapy for insomnia (CBT-I) is an effective treatment for insomnia; however, it remains unclear if this treatment method is effective in improving sleep outcomes and reducing concomitant postconcussion symptoms.

Objective: The hypotheses for this study are that (1) CBT-I will improve sleep outcomes and (2) CBT-I will improve concomitant postconcussion symptoms.

Methods: In total, 40 individuals who are within ≥4 weeks of postconcussion injury and have insomnia symptoms will be enrolled in this randomized controlled trial. Participants will be randomized into either a group that starts a 6-week CBT-I program immediately after baseline or a waitlist control group that starts CBT-I following a 6-week waiting period. All participants will be reassessed 6, 12, and 18 weeks after baseline. Standardized assessments measuring sleep outcomes, postconcussion symptoms, and mood will be used. Linear regression and *t* tests will be used for statistical analyses.

Results: Enrollment of 40 participants was completed July 2022, data collection will be completed in November 2022, and publication of main findings is anticipated in May 2023. It is anticipated that participants experience reduced insomnia symptoms and postconcussion symptoms following CBT-I and these improvements will be retained for at least 12 weeks. Additionally, we expect to observe a positive correlation between sleep and postconcussion symptom improvement.

Conclusions: Successful completion of this pilot study will allow for a better understanding of the treatment of insomnia and postconcussion symptoms in individuals following a concussion.

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International Registered Report Identifier (IRRID): DERR1-10.2196/38608

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KEYWORDS

sleep; concussion; cognitive behavioral therapy; CBT; insomnia; brain; injury; RCT; randomized controlled trial; protocol; recovery; pilot study

Introduction

Background

Between 1.7 and 3.8 million people in the United States experience a concussion each year, and the prevalence of concussions continues to increase [1-3]. A concussion injury results from a rotational or linear force to the head, neck, or face, causing injury to the brain [2,4]. Injuries from a concussion result in a number of symptoms termed *postconcussion symptoms* [5], which can be categorized into 4 different domains: somatic, cognitive functioning, mood regularity, and sleep dysregulation [5].

Sleep dysregulation is a risk factor for prolonged recovery. One recent systematic review found that poor sleep was predictive of poor long-term outcomes in the acute phase of concussion recovery [6], while another systematic review found that poor sleep in the chronic phase of recovery was associated with poor cognitive functioning (executive function and working memory) and emotional regulation [7]. Currently, it is unknown if treatment for sleep disturbances in individuals with a concussion could impact recovery.

The causes of sleep disturbances are multifactorial. Axonal damage that occurs during the concussion injury can result in dysregulation of the sleep and arousal centers in the brain [6,8-11]. Furthermore, medication use, new onset or increase in anxiety or depression, or a change in routine and the sleep schedule can contribute to sleep disturbances [6,12,13]. Sleep complaints can be present immediately following a concussion or within the first few days or weeks following the injury. The most reported sleep disturbance in individuals with a concussion, insomnia, is experienced by nearly 50% of those individuals [14]. Chronic insomnia is defined as difficulty in falling asleep or staying asleep 3 or more days a week for more than 3 months [15,16].

Chronic insomnia following a concussion can result in elevated plasma levels of neurofilament light (NfL) and tau biomarkers [17]. Both NfL and tau biomarkers have been associated with axonal damage, neuronal injury, and neurodegeneration [18]. Additionally, these biomarkers have been associated with cognitive decline and cognitive impairment [18]. Emerging research has found higher levels of plasma NfL and tau biomarkers in individuals with a history of a concussion, who also have poor sleep [19]. A possible mechanism for why these biomarkers are elevated could be disruption in the regular sleep function of metabolic waste clearance through the glymphatic system [19]. It is hypothesized that by improving sleep, metabolic waste clearance within the glymphatic system will be enhanced, which could decrease the accumulation of the NfL and tau biomarkers.

To assist in improving insomnia symptoms, cognitive behavioral therapy for insomnia (CBT-I) is the recommended first-line treatment. CBT-I consists of a multicomponent program that includes cognitive and behavioral strategies targeted to address the perpetuating factors of insomnia [20]. CBT-I is more effective than pharmaceuticals for long-term treatment of insomnia [21,22]. Systematic reviews [23,24] and meta-analyses [25,26] have found that CBT-I has a medium to large effect size in various comorbid populations and diagnoses. A recent scoping review reported that cognitive behavioral therapy (CBT) improved sleep efficiency and sleep quality and reduced insomnia symptoms in individuals with traumatic brain injury of all severities [27]. Furthermore, there was a reduction in concomitant symptoms, specifically anxiety and depression, after completion of the sleep intervention [27].

To date, only one study has evaluated the use of CBT-I in individuals who sustained a concussion [28]. The main findings from this study (n=24) indicated that CBT- I improved insomnia symptoms and sleep quality and decreased dysfunctional beliefs about sleep in adolescents but did not improve anxiety, depression, and postconcussion symptoms following CBT-I. However, a small sample size limits the interpretation of these results. Therefore, an adequately powered clinical trial is needed to evaluate if CBT-I enhances sleep outcomes in people with a concussion and impacts the recovery process.

Objectives and Hypotheses

Aim 1: To Assess the Therapeutic Effect of CBT-I in Individuals With a Subacute Concussion and Symptoms of Insomnia on Sleep Outcomes

We hypothesize that CBT-I will result in a greater magnitude of change in insomnia severity and sleep quality compared to the waitlist control (WLC). Furthermore, we hypothesize that the magnitude of change in insomnia severity and sleep quality will be maintained for 12 weeks following CBT-I.

Aim 2: To Assess the Therapeutic Effect of CBT-I in Individuals With a Subacute Concussion and Symptoms of Insomnia on the Severity and Number of Postconcussion Symptoms, Anxiety, and Depression

We hypothesize that CBT-I will result in a greater magnitude of change in the severity and number of postconcussion symptoms, anxiety, and depression compared to the WLC.

Aim 3: To Evaluate the Relationship Between Improvement in Sleep Outcomes and Postconcussion Symptoms

We hypothesize that improvement in insomnia severity will be positively associated with reductions in the severity and number of postconcussion symptoms.

Exploratory Aim: To Evaluate the Therapeutic Effect of CBT-I in Individuals With a Subacute Concussion

and Symptoms of Insomnia on Levels of NfL and p-tau Biomarkers.

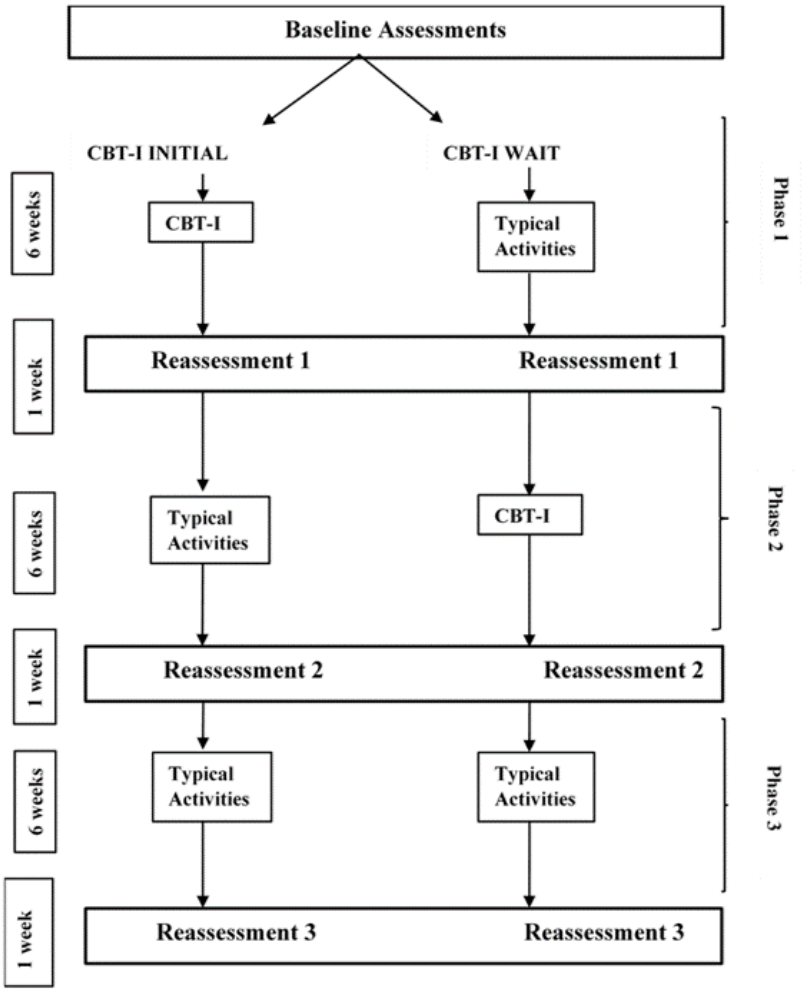
We hypothesize that there will be a significant reduction in plasma NfL and p-tau levels from baseline to post CBT-I.

Methods

Study Overview

The proposed study is a delayed-start randomized controlled trial of 6 weeks of CBT-I among individuals with a concussion, aged 18-64 years old (n=40; Figure 1). Individuals who meet the inclusion criteria (Textbox 1) will be randomized into 2 groups. The first is a CBT-I initial group (CBT-I initial; n=20), which will start the CBT-I intervention directly after completing the baseline assessment. The second group is the WLC group (n=20), which will start the CBT-I intervention 6 weeks after the baseline assessment. The final 6 weeks for all participants, regardless of group assignment, will include participation in typical activities such as maintaining employment status, family roles, etc.

Figure 1. Study flowchart. CBT-I: cognitive behavioral therapy for insomnia.



Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Aged 18 to 64 years
- Within ≥4 weeks of concussion injury
- Self-report difficulty falling asleep, maintaining sleep, or waking up too early at least 3 nights per week since injury
- Score of ≥10 on the Insomnia Severity Index to indicate clinical insomnia [29]
- Score of ≥17 on the Mini-Mental State Examination-Telephone questionnaire [30]

Exclusion criteria:

- Known untreated sleep disorder (such as sleep apnea, restless leg syndrome, circadian rhythm disorder, hypersomnia, or parasomnias)
- Increased risk obstructive sleep apnea (score≥3 on the snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender questionnaire) [31,32]
- Increased risk of restless leg syndrome on the Restless Leg Syndrome Diagnosis Index [33]
- Increased risk of circadian rhythm sleep-wake disorder [34]
- Increased risk of parasomnia [34]
- Active abuse or history (up to 2 years) of alcohol or drug dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria [35]
- Severe mental illness such as schizophrenia or bipolar disorder
- Score of >29 on the Beck Depression Inventory or indication of suicidality (response of “2” or “3” to item 9) [36]
- History of diagnosed nervous system disorders other than concussion (such as multiple sclerosis, Parkinson disease, or stroke)
- Currently works in a night shift

Ethical Considerations

This study was approved by the institutional review board at the University of Kansas Medical Center (STUDY00146439) and was conducted in accordance with the ethical standards of the Helsinki Declaration.

Recruitment

Recruitment will primarily be carried out through physician referral at the concussion management clinic at the University of Kansas Medical Center (KUMC). Potential participants will also be contacted through the KUMC Heron Data Repository/Pioneers participant registry [37]—a registry of patients from the University of Kansas Health System who have given consent to be contacted for potential research. If the number of participants cannot be reached through these primary methods, participants will be sought from other concussion clinics in the Kansas City area, in community support groups, and through social media.

Screening Procedures

Individuals will undergo a 2-step screening process. The first portion will consist of a standard telephone screening, which includes a review of the inclusion and exclusion criteria (Textbox 1); Insomnia Severity Index (ISI) [29] to assess insomnia symptom severity; snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender questionnaire to assess risk of sleep apnea [31,32]; the Restless Leg Syndrome-Diagnostic Index to assess for risk of restless leg syndrome [33]; and the Clinical Interview for Sleep Disorders-Revised [34] questionnaire to assess for circadian rhythm disorders, nightmare disorder, night terror disorder, and REM sleep behavior disorders. The Mini-Mental State Examination Telephone [30,38] will be administered for a cognition screen for informed consent purposes. The second step to the screening process will be to administer the Beck Depression Inventory (BDI) [36] by emailing the potential participant a link to complete the BDI using the Research Electronic Data Capture (REDCap) database [39,40]. The principal investigator, RL, will review the completed BDI to ensure eligibility. If participants are eligible, a link to complete the consent process via REDCap will be emailed to each prospective participant. After the consent process is completed, the participant will be emailed a link to complete the baseline assessments.

Assessments

Overview

The baseline assessments will be sent via a REDCap survey within 2 days of the main consent completion. The baseline evaluation will consist of demographic information collection and a completion of questionnaires to assess sleep outcomes, postconcussion symptoms, and mood.

Demographics

The following demographic data will be collected via self-report during baseline assessment: sex, education level, ethnicity, race, marital status, number of physician-diagnosed concussions, mechanism of concussion injury, list of current medications and dosage of those medications, list of health care services currently receiving, and a question asking if insomnia started before or after the concussion injury.

Sleep Questionnaires

The ISI [29] is a valid and reliable measure of insomnia severity that consists of 7 questions, each rated on a scale of 0-4. The range of scores on the ISI is 0-28; a score of ≥10 suggests clinical insomnia [41]. The ISI completed at screening will be considered the baseline ISI score.

The Pittsburgh Sleep Quality Index (PSQI) will be used to assess quality of sleep [42]. Scores range from 0-21, with a higher score indicating lower quality of sleep. A global score of > 5 indicates poor sleep quality.

Postconcussion Symptom Severity Questionnaires

Postconcussion symptom severity and the number of symptoms will be assessed using the Post-Concussion Symptom Scale (PCSS) [43]. The severity of 22 concussion-related symptoms is assessed on a Likert scale ranging 0-6 with 0="no symptom" and 6="extreme symptom" [44]. A score of 132 is the maximum, indicating that all symptoms are severe [44]. The number of postconcussion symptoms will be assessed by counting the number of symptoms that the participant identified as having a severity of 1 or higher on the PCSS. A score of a 1 indicates that the symptom is mild but still noticeable.

Mood Questionnaires

The BDI [36] assessment will be used to assess the level of depression. The tool consists of 21 items that are scored on a Likert scale of 0-3 with 0="no change in symptom" and 3="severe change in symptom." Scores range from minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe depression (>29).

The BDI completed during screening will yield the baseline BDI score. The Beck Anxiety Inventory (BAI) [45] assessment will be used to assess the level of anxiety. The tool consists of 21 items that are scored on a Likert scale of 1-3 with 0="not at all" and 3="severely." Scores range from minimal anxiety (0-7), mild anxiety (8-15), moderate anxiety (16-25), and severe anxiety (>30).

Blood Plasma Biomarkers

Blood plasma biomarkers will be assessed at baseline for all individuals enrolled and within 1 week of completing the CBT-I intervention. A trained phlebotomist will draw blood (~10 mL) into a vacutainer tube containing EDTA as an anticoagulant. The EDTA tube will then be inverted several times to mix prior to centrifugation at 1500 *g* for 10 minutes at 4 °C. After processing, plasma will be transferred into aliquots and stored at –80 °C until analysis. NfL and p-tau analysis will use Single Molecule Array analytics (Quanterix).

Reassessments

Reassessments will occur 6, 12, and 18 weeks following baseline. Participants will update their current medications and health care services. Additionally, sleep questionnaires, concussion symptoms, and mood questionnaires completed during baseline will be completed at reassessments.

Randomization

Following the baseline assessment, participants will be randomized to either the CBT-I initial group (n=20) or the CBT-I WLC group (n=20; Figure 1). A randomization list was developed using SPSS [46]. Participants are not blinded to their group assignment. One researcher (RL) is providing the treatment for this study and is not blinded to group allocation. Questionnaires are sent to participants via REDCap, and participants will be able to answer the questionnaires on their own time and in their own environment. The same researcher (RL) is also performing data analyses for this study.

The CBT-I Intervention

Overview

The CBT-I program is a 6-week, in-person, one-on-one program conducted by RL, a trained CBT-I provider, and with consultation from a Diplomate in Behavioral Sleep Medicine. The CBT-I will be delivered remotely over a Health Insurance Portability and Accountability Act–compliant teleconference service (Zoom) or via telephone. A standardized CBT-I program will be used [47]. Participants will be given a sleep log to maintain throughout the course of the 6-week intervention. The sleep log will be used to tailor the intervention and to monitor adherence to the intervention for each participant. Each weekly session will start with a discussion on the previous week of sleep, review of the sleep diary, and the prior week's goals. The general session outlines are as follows with each session lasting approximately 45-60 minutes.

Session 1

This session involves gaining a qualitative sleep history, establishing a treatment plan, establishing a sleep schedule and stimulus control, collaborating on strategies for how to stay awake to the prescribed bedtime and what to do if the participant wakes up in the middle of the night, and discussing healthy sleep practices as they relate to a concussion.

Session 2

This session involves reviewing the concepts of circadian rhythm and stimulus control, asking about adherence with possible adjustment to sleep compression bedtime and wake times, and introducing the relaxation techniques of diaphragmatic breathing and deep breathing and their application in daily living.

Session 3

This session involves reinforcing concepts of the circadian rhythm and stimulus control, continuing to monitor the prescribed sleep compression bedtime and wake time, adjusting bedtimes and wake times accordingly, and introducing the relaxation technique of mindfulness and its application in daily living.

Session 4

This session involves continuing to reinforce the ideas of circadian rhythm and stimulus control while monitoring the prescribed sleep compression bedtime and wake time, adjusting bedtimes and wake times accordingly, and introducing the

relaxation technique of progressive muscle relaxation and its application in daily living.

Session 5

This session involves discussing negative sleep beliefs or reinforcing a relaxation technique from previous sessions.

Session 6

This session involves discussing the sleep log and determining if adjustments are needed to the sleep schedule, reviewing the prior week's goals, assessing global treatment gains, and discussing relapse prevention.

WLC Activities

During the wait period portion, the WLC group will be encouraged to continue participation in their typical activities including employment, appointments, and personal schedule. After the 6-week wait period, the WLC group will receive the full CBT-I intervention.

Statistical Analysis

Sample Size

For this study's power analysis, the effect size is set at 0.8, which is based on a prior study that had large effect sizes on insomnia (0.8) [28]. The SD is set at 1 and the α is set at .05. Therefore, the required sample size is 32 participants, which is anticipated on the basis of clinical experience that 10%-25% of participants will drop out of the study so an additional 8 participants will be enrolled; thus, 40 participants will be enrolled for a total of 20 participants in each group. Intention-to-treat analyses will be used; hence, in the event of a participant dropping out after randomization, the data from their last assessment will be carried forward to the reassessment [48].

Statistical Approach

Aim 1: To Assess the Therapeutic Effect of CBT-I in Individuals With a Subacute Concussion on Insomnia Symptoms and Sleep Quality

An independent samples *t* test will be used to determine if there is a significant difference in percent change in the ISI (primary outcome) and PSQI between the CBT-I and the WLC conditions. To assess maintenance for each group, paired *t* tests will be used to determine if there is a significant difference at the following time points: from the reassessment following CBT-I (reassessment 1 for the CBT-I group; reassessment 2 for the WLC group) to the immediate reassessment following the typical activities period (reassessment 2 for the CBT-I initial group; reassessment 3 for the WLC group), and from reassessment following CBT-I to delayed reassessment (reassessment 1 to reassessment 3 for CBT-I group). The percentage of participants who meet the minimal clinically important difference (MCID) will also be reported (7 points for the ISI [36] and 3 points for the PSQI [39]). In the event that the data do not meet the assumptions for parametric *t* tests, nonparametric tests (Mann-Whitney *U* test for independent samples, and Wilcoxon signed rank test for paired samples) will be used.

Aim 2: To Assess the Therapeutic Effect of CBT-I in Individuals With a Subacute Concussion on the Severity and Number of Postconcussion Symptoms, Anxiety, and Depression

An independent samples *t* test will be used to determine if there is a significant difference in percent change for the PCSS, BAI, and BDI between the CBT-I condition and the WLC group. To assess maintenance, paired samples *t* tests will be used to determine if there is a significant difference from the following time points: from the reassessment following CBT-I (reassessment 1 for the CBT-I group; reassessment 2 for the WLC group) to the immediate reassessment following the typical activities period (reassessment 2 for the CBT-I Initial group; reassessment 3 for the WLC group), or from reassessment following CBT-I to delayed reassessment (reassessment 1 to reassessment 3 for the CBT-I group). The percentage of participants who meet the MCID criteria for each outcome will be reported (12 points for the PCSS, 4 points for the total number of symptoms on the PCSS, 4 points on the BAI, and 5 Points on the BDI [40,45,46]). In the event that the data do not meet the assumptions for parametric *t* tests, nonparametric tests (Mann-Whitney *U* test for independent samples and Wilcoxon signed rank test for paired samples) will be used.

Aim 3: To Evaluate the Relationship Between Improvement in Sleep Outcomes and Postconcussion Symptoms

Two simple linear regressions will be run to evaluate the relationship between improvement in sleep outcomes and postconcussion symptoms. The first simple linear regression will determine if change in ISI from preintervention to postintervention stages (predictor variable) will predict changes in postconcussion severity (dependent variable). The second simple linear regression will determine if change in the ISI from preintervention to postintervention stages (predictor variable) will predict changes in the number of postconcussion symptoms (dependent variable). If there are significant differences at baseline in age, gender, medication use, number of concussions, and receiving other services between the two groups, the variables will be entered into the model as a covariate, and the 2 models will be rerun.

Exploratory Aim: To Evaluate the Therapeutic Effect of CBT-I in Individuals With a Subacute Concussion and Symptoms of Insomnia on Levels of NfL and p-Tau Biomarkers

Paired samples *t* tests will be used to determine if there is a significant change in NfL and p-tau plasma levels before and after the CBT-I intervention. In the event that the data do not meet the assumptions for parametric *t* tests, nonparametric tests (Mann-Whitney *U* test for independent samples and Wilcoxon signed rank test for paired samples) will be used.

Results

Enrollment of 40 participants was completed in July 2022, data collection is anticipated to be completed in November 2022, and publication of main findings is anticipated in May 2023. After final data analysis and writing of the results, the manuscripts will be submitted to appropriate journals for

dissemination. It is expected that participants in this study will experience a reduction in insomnia symptoms and an increase in sleep quality after CBT-I, and these improvements in insomnia symptoms and sleep quality will be retained following the intervention. Additionally, it is expected that the therapeutic effect of CBT-I will result in an improvement in postconcussion symptom severity and the number of symptoms. Improvement in insomnia severity will predict improvement in the severity and number of postconcussion symptoms. It is also anticipated that there will be a reduction in plasma NfL and p-tau levels following the CBT-I intervention.

Discussion

Expected Findings

It is anticipated that individuals who complete CBT-I will have improved sleep outcomes as well as reduced postconcussion symptoms. Additionally, it is anticipated CBT-I will reduce NfL and p-tau levels. This study may modify the traditional approach to postconcussion care by asserting that insomnia can be resolved by CBT-I and that improvement in insomnia symptoms is associated with improvement in postconcussion symptoms. The use of CBT-I in individuals with a concussion is relatively novel as there is currently only one published pilot randomized controlled trial [28]. Additionally, the biomarker substudy will provide valuable insights into the mechanisms of how sleep assists in neuronal recovery. This study provides both a mechanistic and clinical perspective for the treatment of individuals with postconcussion symptoms.

The number and severity of symptoms following a concussion vary among individuals [49,50,51,52]. In the majority of concussion cases, 80%-90% of individuals experience symptom resolution between 1 and 3 weeks post injury [1,4,5,53]. However, for the remaining 10%-15% of concussion cases, symptoms persist for months to years post injury [54-57]. Combined, approximately 50% of individuals recovering from a concussion have insomnia symptoms [14], and 10%-15% of people have prolonged recovery. Therefore, there is a high percentage of individuals who would benefit from standard use of CBT-I to resolve their insomnia symptoms and mitigate their postconcussion symptoms.

This study also offers a potential insight into the mechanism of how improvement in sleep assists in neuronal recovery and the possible prevention of neurodegeneration. One marker for recovery could be the presence of NfL in p-tau as these markers are associated with neuronal injury and neurodegeneration. Further exploration of the presence of these biomarkers may provide valuable information on how significant symptoms of insomnia affect recovery and how those biomarker levels respond with improvement in sleep following CBT-I intervention.

Anticipated Limitations

Potential limitations related to the treatment response are as follows. First, it is unknown how each participant will respond to the CBT-I treatment with their current symptom burden. Enrolling participants who are within at least 4 weeks of their concussion was to obtain individuals who have relatively stable symptoms at the time of enrollment. Second, medication use and dosage may affect the treatment response to the CBT-I intervention. Therefore, information on medication will be collected at baseline and at reassessments to be included in statistical analysis if indicated. Third, participants will potentially be receiving care from other health care providers, which could impact the interpretation of the results. Therefore, information on type of services being received will be collected at baseline and at reassessments to be included in statistical analysis if indicated.

Another potential limitation to this study is attrition. The attrition rate was 20% in one study evaluating CBT-I in adolescents with a concussion [28]. A 20% attrition rate was also observed in a cognitive behavioral intervention study on adults who have had a concussion [58]. To account for attrition, we will overenroll by 20% in this study. To help with retention, study procedures and time commitment will be clearly articulated to potential participants and reinforced during the course of the study. Furthermore, individuals in the WLC will be contacted by telephone in the middle of their 6-week waiting period to remind them of their upcoming CBT-I sessions and to maintain connection and interest.

Conclusions

Insomnia is the most common sleep disturbance in individuals recovering from a concussion. This study is the first randomized control trial to evaluate if CBT-I improves sleep outcomes and postconcussion symptoms. Potential results from this study could indicate that improvement in sleep may improve postconcussion symptoms—this could be insightful research to improve both clinical care and progress clinical research in the concussion community. Future studies need to continue to evaluate (1) the mechanistic response to improvement in sleep and (2) the relationship between improved sleep and improved recovery from postconcussion symptoms.

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Data Sharing

The data sets generated and analyzed in this study may be available from the corresponding author upon reasonable request.

Conflicts of Interest

CS is the owner and chief executive officer of Sleep Health Education, LLC.

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Abbreviations

BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
CBT: cognitive behavioral therapy
CBT-I: cognitive behavioral therapy for insomnia
ISI: Insomnia Severity Index
KUMC: University of Kansas Medical Center
NfL: neurofilament light
PCSS: Post-Concussion Symptom Scale
PSQI: Pittsburgh Sleep Quality Index
REDCap: Research Electronic Data Capture
WLC: waitlist control

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Protocol

Usability and Effectiveness of an Individualized, Tablet-Based, Multidomain Exercise Program for People With Dementia Delivered by Nursing Assistants: Protocol for an Evaluation of the InCoPE-App

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Abstract

Background: The COVID-19 pandemic has had drastic consequences on everyday life in nursing homes. Limited personnel resources and modified hygiene and safety measures (eg, no external exercise instructors, no group settings) have often led to interrupted physical exercise treatments. As a consequence, people with dementia benefiting from individualized exercise programs are affected by the pandemic's impact.

Objective: Our goal is to develop an easily applicable mobile application (Individualized Cognitive and Physical Exercise [InCoPE] app) allowing nursing assistants to test cognitive function and physical performance and subsequently train people with dementia through a multidomain, individualized exercise program.

Methods: We will evaluate the usability and effectiveness of the InCoPE-App by applying a mixed method design. Nursing assistants will use the InCoPE-App for 18 weeks to assess the cognitive function and physical performance of 44 people with dementia every 3 weeks and apply the individualized exercise program. We will record overall usability using questionnaires (eg, Post-Study System Usability and ISONORM 9241/10), log events, and interviews. Perceived hedonic and pragmatic quality will be assessed using the AttrakDiff questionnaire. Effectiveness will be evaluated by considering changes in quality of life as well as cognitive function and physical performance between before and after the program.

Results: Enrollment into the study will be completed in the first half of 2022. We expect an improvement in the quality of life of people with dementia accompanied by improvements in cognitive function and physical performance. The usability of the InCoPE-App is expected to be rated well by nursing assistants.

Conclusions: To date, there is no scientifically evaluated app available that enables nursing assistants without expertise in sports science to deliver an individualized exercise program among people with dementia. A highly usable and effective InCoPE-App allows nursing assistants to test cognitive function and physical performance of people with dementia and, based thereon, select and deliver an appropriate individualized exercise program based on the cognitive and physical status of an individual, even in times of a pandemic.

Trial Registration: German Register of Clinical Trials DRKS00024069; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00024069

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KEYWORDS

institutionalization; institutionalized; sport; physical activity; fitness; exercise; dementia; digital application; cognitive performance; physical performance; cognitive function; physical function; cognitive decline; nursing home; long-term care; usability; effectiveness; mHealth; mobile health; health app

Introduction

The COVID-19 pandemic has had drastic consequences for all areas of everyday life. In many nursing homes, routine processes had to be changed. Some activities and treatments were reduced or, in areas, canceled. Hygiene and safety measures (eg, no external exercise instructors, no group settings) and the increased workload for nursing assistants led to suspending physical exercise programs and activities, especially when delivered in a group setting. The potential consequences for nursing home residents include reduced general activity accompanied by decrease in cognitive function and physical performance and a considerable loss of an individual's quality of life. Furthermore, these COVID-19–induced changes may also have an economic impact and may increase care expenses in the long term.

Dementia is present in up to 50% of nursing home residents [1]. The clinical symptoms of this neurodegenerative disease include, but are not restricted to, decreased cognitive skills and reduced physical performance (eg, balance and mobility) [2,3]. Many people with dementia experience a rapid progression of the disease [1]. Thus, people with dementia might be seriously affected by COVID-19–induced reduction of physical or mentally stimulating activities and similar treatments (eg, physiotherapy, ergo therapy, social interactions) in nursing homes.

In light of the absence of medication to cure dementia, physical activity is one of the major nonpharmacological interventions that has become very important in treating people with dementia. Previous reviews have mainly reported positive effects of physical activity on cognitive but also physical outcomes in people with dementia [4-8]. However, conclusive evidence is still lacking, mainly due to limited numbers of high-quality studies and large heterogeneity in methods and exercise program parameters (eg, scope, duration, intensity, contents, settings). Of note, an individual's prior exercise experiences and preferences may also contribute to the success of an intervention. These factors, combined with the older age of people with dementia as well as the different stages and degrees of impairment, result in the highly heterogeneous samples often found in research studies. To elicit the potential effects of physical activity interventions in people with dementia, we have previously argued that individualization of the exercise program may thus be crucial [9]. To the best of our knowledge, individualized exercise programs are not sufficiently included in routines of nursing homes, and optimal or successful ways of distribution have not been reported in prior research studies.

Fundamental changes in health practice are driven by recent developments in interactive health technologies that promote health and manage illness [10]. These technologies have been reported to elicit beneficial health outcomes in various settings (eg, physical activity coaching app for breast cancer [11], Partners in School Asthma Management for inner-city elementary school children [12]). The number of digital health apps has increased exponentially, whereas the number of publications addressing their usability evaluation has remained at a low level [13]. There is still a lack of reports on the development and usability processes during app development in digital health settings. More than 95% of apps available today have not been scientifically tested, and the limited number of controlled trials of mobile technology interventions reported only modest effects [14]. However, usability is a crucial component of good practice in the development of digital apps [15]. End users' needs are particularly important in digital health applications to ensure that individuals affected by any health issue can use the intervention appropriately, which may in turn lead to greater acceptance and thus efficiency of the intervention [16]. The ISO standard 9241-11 defines usability as the extent to which a product can be used to achieve the specified goals with effectiveness, efficiency, and satisfaction [17]. Another standard on software quality, ISO 25010, includes attributes for usability such as understandability, learnability, operability, and attractiveness [18].

Our team will develop a tablet-based mobile app aimed at supporting nursing assistants to (1) test the cognitive function and physical performance of people with dementia and (2) subsequently train people with dementia. The training is a multidomain, individualized exercise program that will be adjusted to the individual's current physical and cognitive performance with the focus of improving physical and cognitive performance in the short and long term. In times of COVID-19, this is a novel and innovative approach that allows nursing homes to maintain a physical activity routine while complying with hygiene and safety measures, as no external exercise instructor is needed. The individualization approach used in this study in combination with the direct applicability in the setting of nursing homes is promising in terms of the individual benefit of the exercise program on physical and cognitive performance as well as quality of life. The aim of the present study is to evaluate the usability and effectiveness of the individualized exercise program provided by the Individualized Cognitive and Physical Exercise (InCoPE)-App.

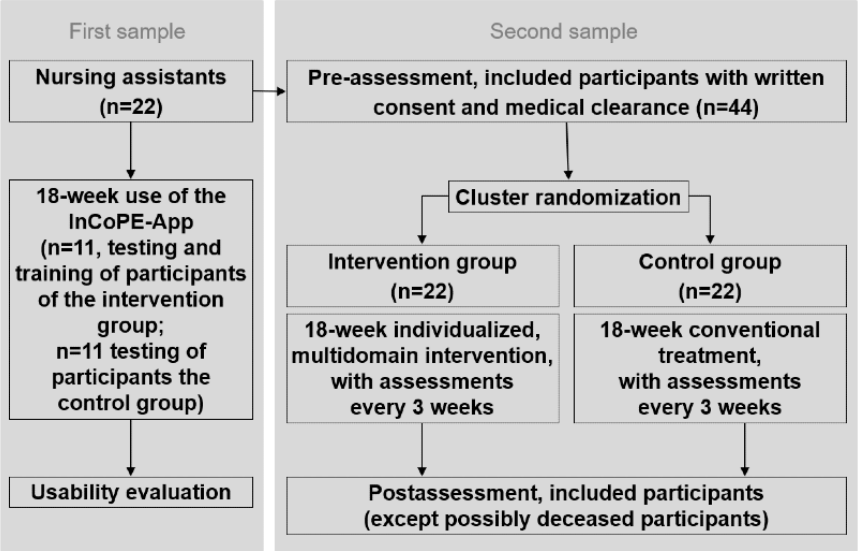
Methods

Study Design

This study combines the evaluation of the usability of the InCoPE-App with the effectiveness of the individualized exercise program concerning cognitive function, physical performance, and quality of life. Thus, a mixed methods design with different methodological components will be used. The evaluation of the usability and effectiveness of the InCoPE-App will be based on the use of the app for a duration of 18 weeks in a nursing home setting. This approach represents a field study and will be carried out as a cluster-randomized controlled trial in which the InCope-App will be used with people with

dementia and the individualized, multidomain exercise program will be delivered by nursing assistants with the help of the app. The nursing homes will be cluster randomized, and each nursing assistant will subsequently recruit at least 2 people with dementia (see Figure 1).

Figure 1. Flow of participants. InCoPE: Individualized Cognitive and Physical Exercise.



Ethical Approval

The study is conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Karlsruhe Institute of Technology (Karlsruhe, Germany).

Participants

To evaluate the InCoPE-App in terms of usability and effectiveness, 2 different study samples are required (see Figure 1). The first sample will include the future users of the InCoPE-App (ie, nursing assistants). To this end, initial contact will be established through the heads of care facilities in southwestern Germany who suggest potentially interested nursing assistants, who will subsequently receive detailed information about the aims and the content of the study. The following inclusion criteria must be fulfilled: (1) willingness to participate in the training to familiarize themselves with the InCoPE app, (2) command of the German language as the InCoPE-App is only available in German at this time, and (3) employment at the nursing home for at least 18 weeks. External employees (eg, physical therapists) will be excluded.

The second sample will include participants with primary dementia living in nursing homes. This sample will be drawn to evaluate usability and trends toward the effectiveness of the individualized exercise program as delivered by the InCoPE app. Participants in the second sample will be selected by nursing assistants. Before entering the study, written consent by participants or their legal guardians will be obtained. Prior to the intervention, a clearance certificate from the participant's general practitioner will be collected, which will also include information about the dementia diagnosis and other pertinent information such as medication intake and comorbidities. Additional inclusion criteria are (1) Alzheimer disease, vascular dementia, or other primary dementia; (2) mild to moderate stage of dementia (Mini-Mental State Examination [MMSE]: 10-24); (3) age older than 65 years; and (4) walking ability of at least 10 meters with or without a walking aid. Exclusion criteria include (1) secondary dementia, (2) other severe cognitive impairments, (3) other severe neurological conditions, (4) other severe acute diseases, and (5) severe motor impairments.

Intervention

The individualized exercise program for people with dementia is based on earlier work by this research group and includes a combination of cognitive and physical exercises [19]. The included exercises were further differentiated to ensure a higher degree of individualization following the idea of individualized medicine [20]. The individualized exercise program is embedded in the InCoPE-App, which will be utilized by nursing assistants. The InCoPE-App will be installed on a tablet device (Android), and nursing assistants will be trained in the appropriate use of the app in order to test and instruct people with dementia. The training comprises theoretical online modules for self-study (eg, theoretical basics of physical exercise with people with dementia, objective testing of physical and cognitive performance in people with dementia, first steps with the InCoPE-App) and 2 face-to-face meetings (between project members or research staff and nursing assistants) for the usage of the InCoPE-App. The InCoPE-App contains detailed photographic materials and descriptions to offer visual support in the execution of the proposed tests and exercises.

The tests assessing motor and cognitive performance included in the InCoPE-App are based on published recommendations and were used with people with dementia before [21,22]. On the basis of cluster analysis in a large sample of people with dementia who participated in our group's previous randomized controlled trial [19], we identified 4 homogeneous subgroups of people with dementia [23] who were also considered when we designed the InCoPE-App: participants with (1) below-average motor and cognitive performance, (2) average cognitive performance and above-average motor performance, (3) above-average cognitive and motor performance, and (4)

above-average cognitive performance and below-average motor performance. The initial testing of physical and cognitive performance included in the InCoPE-App will be used to determine whether an individual belongs to cluster 1, 2, 3, or 4. Testing will be repeated every 3 weeks during the 18-week intervention period to allow the InCoPE-App to regularly adjust the duration, intensity, and contents of the cognitive and physical exercises based on the individual's needs. We anticipate that the desired physical and cognitive adaptation to the exercise program will be achieved by gradually increasing exercise difficulty and intensity (eg, number of repetitions).

For each individual, the content of the individualized exercise program will vary based on the cluster categorization. For example, a person in cluster 1 will receive recommendations to complete exercises that focus on increasing balance, mobility, and strength as well as cognitive stimulation. In contrast, a person in cluster 4 will likely undergo exercise with a more pronounced focus on balance, mobility, or strength regardless of the degree of cognitive stimulation. Furthermore, promotion of endurance is part of every training session. The differentiation of each exercise is regulated via several degrees of difficulty and intensity. Moreover, additional cognitive input is subdivided into 3 levels of difficulty. Training sessions will take place twice per week on nonconsecutive days for 60 minutes. These 60 minutes are divided into a ritualized warm-up, first combination of exercises, short break with ritualized exercises for balance, second combination of exercises, and cooldown. Pure training duration will be about 40 minutes. The ritualization of training sequences will give the people with dementia a sense of security.

Outcomes

Primary Outcomes

The primary outcomes were defined along the overall aim to evaluate the usability and effectiveness of the individualized exercise program delivered via the InCoPE-App. In Table 1, the questionnaires and measures for usability, quality of life, and overall cognition as well as methods to evaluate executive function and physical performance are listed.

Table 1. Primary outcomes.

Dimensions	Assessments	Pre	Post	Implemented in the InCoPE[a]-App
Overall usability	Post-Study System Usability Questionnaire (PSSUQ) version 3 [24]	No	Yes	No
Overall usability	ISONORM, a questionnaire that operationalizes the 7 criteria of EN ISO 9241-10 [25]	No	Yes	No
Perceived hedonic and pragmatic quality	AttrakDiff 2 [26]	No	Yes	No
Quality of life	German Quality of Life-Alzheimer's Disease (QOL-AD) [27]	Yes	Yes	No
Global cognition	Mini-Mental State Examination Test (MMSE) [28]	Yes	Yes	Yes
Executive function	Digit span [29]	Yes	Yes	Yes
Mobility	Timed Up & Go (TUG) test [30]	Yes	Yes	Yes
Mobility	6-meter walking test (6MWT) [31]	Yes	Yes	Yes
Function and strength of lower limbs	Modified 30-second chair stand test (CST) [32]	Yes	Yes	Yes
Balance	Frailty and Injuries: Cooperative Studies of Intervention Techniques-subtest 4 (FICSIT-4) [33]	Yes	Yes	Yes

[a]InCoPE: Individualized Cognitive and Physical Exercise.

Each nursing assistant will use the app to deliver the individualized exercise program within the 18-week intervention to 2 people with dementia. The overall usability will be assessed after the intervention using the Post-Study System Usability Questionnaire (PSSUQ) [24]. The PSSUQ gives insight into user satisfaction with a system (eg, system usefulness, information quality, and interface quality). This questionnaire can be considered a useful tool for field studies [24]. We will use PSSUQ version 3, which is comprised of 19 items such as system usefulness, information quality, and interface quality rated on a 7-point Likert scale (1: strongly agree to 7: strongly disagree) [24,34]. Furthermore, usability will be assessed using the ISONORM questionnaire [25], which covers the implementation of the 7 defined criteria based on the International Ergonomics Standard DIN EN ISO 9241-110. This questionnaire operationalizes the 7 criteria of the EN ISO 9241-10 and was developed to evaluate software development [35]. The completion of the questionnaire takes 10 minutes, and bipolar statements from 35 items are assessed using a 7-point Likert scale (1: very negative to 7: very positive) [35]. The perceived hedonic and pragmatic quality of the InCoPE-App will be assessed using the AttrakDiff 2 questionnaire [26]. This questionnaire evaluates the participants' perceptions of the InCoPE-App by means of semantic differentials.

Examination of the effects of the InCoPE-App on physical and cognitive performance in people with dementia will be determined based on the listed variables in Table 1. The primary outcomes will be assessed before and after the 18-week intervention. To assess quality of life, the 13-item caregiver-administered version of Quality of Life-Alzheimer's Disease (QOL-AD) [27] will be applied. The QOL-AD is a valid and reliable tool (internal reliability, α=0.88-0.89; test-retest reliability for caregivers, 0.92) [27]. Global cognition will be assessed with the MMSE [28]. The questionnaire will

be implemented in the InCoPE-App. The MMSE easily assesses 7 areas of cognitive function, with sufficient test-retest reliability (0.80-0.95) [28,36]. To assess executive function, the Digit Span Test [29] will be administered. The Digit Span Test consists of 2 parts: forward and backward. Participants will be asked to repeat a sequence of 3 to 9 digits forward and of 2 to 8 digits backward. The InCoPE-App will be used to document the given answers. The Digit Span is a reliable and valid test [37].

The Timed Up & Go (TUG) test will be conducted by asking participants to rise from a chair, walk 3 meters, turn around, and then go back and sit down again on the chair [30]. Nursing assistants will instruct participants while using the InCoPE-App to assess the time taken by each participant. Time is measured from the initial impulse to stand up until participants are seated again. Everyday walking aids are allowed. For the 6-meter walk test (6MWT) [31], participants will be asked to walk from one side of the room to the other side, where the distance of 6 meters will be marked using start and finish lines on the floor. When participants cross these lines, the time required to walk 6 meters will be measured using the InCoPE-App. In front of the starting line and behind the finish line, participants will have about 2 meters for acceleration and deceleration. If needed, participants are allowed to use their walking aids. Strength and function of lower limbs will be assessed using the modified 30-second chair stand test (30s CST). For the modified 30s CST, participants will be asked to stand up from a chair (height 46 centimeters, with armrests) as often as possible for 30 seconds. The modified version allows the use of armrests [32], which is essential for the majority of older adults with dementia to safely perform this test. While testing lower extremities, no walking aids are allowed. Static balance will be determined using the Frailty and Injuries: Cooperative Studies of Intervention Techniques- subtest 4 (FICSIT-4) [33], in which participants are asked to perform 4 different standing positions (Romberg, semitandem, tandem, and single leg) for 10 seconds without walking aids or other assistance. The FICSIT-4 performance is rated on a scale of 0 to 5 points. If participants cannot hold the first position for at least 3 seconds, a score of 0 is given. In contrast, participants receive a score of 5 if they are able to stand in the most difficult (ie, single leg) position for at least 10 seconds.

The chosen tests for physical performance are considered reliable tests in a geriatric setting. Among people with dementia, the intraclass correlation coefficients for test-retest reliability are 0.79-0.82 for FICSIT-4, 0.83-0.89 for 6MWT, 0.78-0.88 for the modified 30s CST, and 0.72-0.99 for the TUG test [38,39]. The 95% minimal detectable changes are 58.9%-71.1% for FICSIT-4, 31.6%-41.5% for 6MWT, 33.2%-45.7% for the modified 30s CST, and 15.8%-39.6% for the TUG test [38,39]. No information about content and construct validity is available in this setting.

Secondary Outcomes

Data used to determine the usability as well as the subcategory of feasibility will be assessed through multiple methods (see Table 2). These methods help to get deeper insight and can improve the reliability and validity of the findings [40]. We will combine quantitative (ie questionnaires, task completions, and log events) and qualitative (ie, interviews and field notes) methods to produce a rich data set, which is especially recommended in health informatics research [41,42].

Table 2. Secondary outcomes of the usability measures and logged events as well as requested information measures.

Content	Recording method
Field notes (eg, participation in tests and training)	Qualitative and quantitative analysis
Interviews on satisfaction	Qualitative analysis
Number of completed training sessions	Quantitative output of the InCoPE[a]-App
Number of successfully completed testing periods	Quantitative output of the InCoPE-App
Number of rejected exercises	Quantitative output of the InCoPE-App
Kind of rejected exercises	Quantitative output of the InCoPE-App
Mean and range of the actual duration of the tests and the training sessions	Quantitative output of the InCoPE-App
Number and content of telephone calls	Qualitative analysis
Number and content of emails	Qualitative analysis
Satisfaction with the training session	Request after training session
Participation of the participant	Request after training session

[a]InCoPE: Individualized Cognitive and Physical Exercise.

Several forms of field notes, such as participation of participants after each test and exercise session, will be documented during the whole intervention. Additionally, nursing assistants will be asked to submit feedback, and we will regularly get in touch with nursing assistants by phone calls and emails to identify possible problems that arise when delivering the individualized exercise program through the InCoPE app.

The logged events and other pertinent information (see Table 2) are a substantial part of the usability with their subgenre feasibility. These feasibility measures place focus on app contents instead of human-technology interface. The feasibility measures are used to assess practicality and satisfaction as well as acceptance of the individualized exercise program but also the respective exercises and the testing. To this end, variables

aimed at the exercises, testing, and participation will be collected by analyzing logged events during the entire 18-week intervention.

Interviews will focus on satisfaction with the InCoPE-App. The open-ended approach of Georgsson and Staggers [43] will serve as reference to ask users about aspects of the InCoPE-App, ranging from good to poor usability. We will ask 3 questions: (1) What parts of the system did you think were well designed? (2) Which parts of the system did you think were inadequately designed? (3) Do you have any other comments about the system functions and regarding its usability? All interviews will be conducted on a guided basis and will be held in German. With informed consent of the participants, the interviews will be recorded using a voice recorder (Philips DVT2050, Eindhoven, Netherlands).

Additional secondary outcomes will be assessed to obtain a holistic view of the participants who will be trained with the InCoPE-App. These physical and sociodemographic variables and respective assessment tools are presented in Table 3.

Table 3. Secondary outcomes on physical and sociodemographic information.

Dimensions	Assessments	Pre	Post	Implemented in the InCoPE[a]-App
Grip strength	Balloon manometer [44]	Yes	Yes	Yes
Frailty	Standardized phenotype of frailty in older adults [45]	Yes	No	Yes
Pain	Single item	Yes	Yes	Yes
Sociodemographic data and medical information	Singe item	Yes	No	No
Body height and weight	Single item	Yes	No	Yes
Fear of falling	FES-I[b] [46]	Yes	No	No

[a]InCoPE: Individualized Cognitive and Physical Exercise.

[b]FES-I: Falls Efficacy Scale International Version.

Grip strength is measured with a balloon manometer [44]. Participants sit on a chair without armrests and solid feet-to-floor contact. Participants will be instructed and verbally encouraged to squeeze the balloon as hard as possible. Both hands will be tested. While being tested, participants should keep the upper arm in contact with the trunk and flex the elbow 90°. Additionally, the wrist is held in a neutral position (thumb up). To examine frailty, the Fried Frailty Criteria will be used [45]. Body weight, self-reported exhaustion, grip strength, walking speed, and level of physical activity in the past 3 months will be assessed before and after the intervention.

Nursing assistants will ask the participants for their body height and weight and enter them directly into the InCoPE-App. Fear of falling will be measured with the German version of the Falls Efficacy Scale International Version (FES-I). The questionnaire consists of 16 items rated on a 4-point scale that are combined into a total score. High values indicate a high fear of falling. Several studies have reported this instrument's high reliability and validity [46].

Sample Size

The sample size for the number of nursing assistants who will evaluate the InCoPE-App with regard to usability was defined using a probabilistic model of problem discovery for formative user research [34]. We defined a sample size comprising 22 participants to have a 90% chance of observing with a probability of 0.1. In the second study phase, outcomes also include usability in addition to the effectiveness of the InCoPE-App with respect to adaptations in physical and cognitive performance in people with dementia. For this reason, each participant will recruit 2 appropriate residents with dementia in accordance with our inclusion and exclusion criteria. We anticipate that our calculated sample size (N=44: intervention group [IG], n=22; control group [CG], n=22) will be appropriate to examine potential trends toward effectiveness of the InCoPE-App.

This sample size allows detection of moderate effects calculated using an ANOVA with repeated measures for within and between interactions. The calculation of the sample size with G*Power version 3.1.9.2 (Heinrich Heine University of Dusseldorf, Germany [47]; effect size $\eta p^2 = 0.07$, α error probability .05, power 0.95) resulted in 44 participants.

Randomization and Concealment

The residents with dementia recruited by nursing assistants will be allocated to either the CG or IG. This allocation will be performed by cluster randomization as it is not possible to blind participants, nursing assistants, or study personnel regarding group allocation. Participants in the CG will only receive conventional treatment such as individualized medication, standard care, or therapeutic applications for 18 weeks. Participants in the IG will receive the individualized exercise program in addition to conventional treatment. To ensure equal conventional treatment for the IG and CG during the intervention, it will be continuously documented.

Data Management

Patient Documentation

The flow of participants will be organized and documented with an Excel documentation file. The participating nursing assistants will be assigned a 2-digit ID (pseudonymization of the data). All personally identifiable information will be documented in a separate Excel file and will be stored separately. The residents with dementia trained by nursing assistants will receive a 3-digit ID, where the first digit will encode the assignment to IG or

CG. The collection and storage of the data will be performed separately. Only selected members of the project team will have access to uncoded data. The InCoPE-App is not connected to the internet to ensure security of personal data during the study. After the end of the 18-week intervention, collected data will be transferred manually via cable and manually stored on a computer that is not connected to the internet.

The collection and retrieval of the data from the questionnaires focusing on usability will be done manually (paper and pencil) and via SoSciSurvey. The entered data will be checked for completeness, validity, and plausibility by a member of the research team.

Data Monitoring

This study represents a non-drug intervention focusing on health benefits among people with dementia while undergoing an individualized exercise program delivered by trained nursing assistants who use the InCoPE-App. We do not expect any harmful effects nor adverse events related to the individualized exercise program. All exercises that are part of the program have been used in people with dementia before, and all questionnaires used to examine usability are derived from validated instruments that have been widely used in prior research. The study is thus considered to have minimal to no risks for participants, and establishing a data monitoring committee is not required. An interim analysis is not planned.

Statistical Methods

All analyses will be performed using SPSS 27.0 (IBM Corp, Armonk, NY). Prior to analysis, plausibility (eg, considering range and distribution) will be checked to minimize errors. The quantitative analysis comprises the evaluation of the usability questionnaires, which will be analyzed with respect to the corresponding guidelines and will be compared with representative data.

The baseline values of physical and cognitive performance will be compared between IG and CG using chi-square tests for categorical data, Mann-Whitney *U* tests for nonparametric variables, and t tests for continuous and normally distributed parameters. Normal distribution will be checked with the Shapiro-Wilk test. Means and standard deviations will be calculated for normally distributed data, and medians and interpercentile ranges will be calculated for non-normally distributed data. A 2-factor ANOVA with repeated measurement will be used to identify treatment effects. In addition, 95% confidence intervals and partial Eta^2 will be calculated. The log events will be summarized and analyzed descriptively. Potential effects among subgroups based on varying physical or cognitive performance, gender, fear of falling, and logged events (completed training sessions, average duration of the training sessions) will be investigated using chi-square tests and *t* tests.

Qualitative content analysis of the field notes will be conducted [48]. The interviews will be fully transcribed and checked for accuracy. The entire coding process will be independently performed by 2 scientists. The transcripts will be reviewed to identify meaningful content-related aspects. These aspects will be systematically described using a category system. Research questions and interview guidelines will be consulted to deductively derive the main categories. Subcategories will be inductively developed based on the findings (eg, by subsumption). The category system will be tested by 2 scientists who will independently test-code several parts of the qualitative material and subsequently adapt the categories and their definitions. The 2 coding systems will eventually be merged by consensual coding where consensus will be reached.

Results

Enrollment for the study started in October 2021. We plan to complete the postassessments of the last included nursing home in April 2022. Results are expected to be available in the second half of 2022.

Discussion

Summary

Physical activity in addition to conventional treatment can have a beneficial impact on cognitive and physical performance as well as quality of life in people with dementia. Providing scientifically grounded and individualized, multidomain exercise programs is challenging within everyday nursing care. The digital application InCoPE-App enables nursing assistants to regularly test cognitive and physical performance and subsequently train people with dementia based on their individual performance levels. We expect that the individualization of the exercise program as well as regular use ensured by high usability will result in increased physical and cognitive performance as well as quality of life in people with dementia after the 18-week program delivered by the InCoPE app. The increase in cognitive and physical performance may further ease the care demands and needs of people with dementia and thus possibly reduce the workload of nursing assistants.

Strength and Limitations

Through the innovative and timely development method and thorough evaluation and integration of users' experiences [49], we expect an application that is highly usable and feasible in everyday care situations. The acceptance of the InCoPE-App will promote its regular usage and thus allow testing and training residents with dementia individually. The regular conduct of physical and cognitive tests that is implemented as an essential part of the app will help to document the progression of disease symptoms and can thus be regarded as an additional objective tool for clinical documentation, which is required on a regular basis in a nursing home setting. The individualization of the exercise program, which has been described as critically important in previous research [9,20], is the key innovative and novel component of the InCoPE-App.

It is unlikely but possible that usability of the InCoPE-App will be rated as low by nursing assistants. In this case, fundamental changes within the application will be required to increase acceptance and practicability, which may have a considerable impact on the effectiveness of the exercise program. There are risks from a technical point of view that might impede the usability of the InCoPE-App, such as possible failure of the tablets to store the data on each tablet. To lower this risk, we will provide the required tablet with the installed InCoPE-App

for each participating nursing home. In addition, nursing assistants can contact the research team to report technical issues and get help at any time.

Another limitation is the rather small number of participating people with dementia. This sample size is sufficient to detect moderate within and between interactions. However, it might be too small to statistically detect small effects. The use of the InCoPE-App within everyday life allows us to gain information about everyday feasibility and suitability; thus, results can be more easily transferred to daily routine.

Dissemination

A manuscript with the results on usability and effectiveness based on the primary outcomes will be published in a peer-reviewed journal. Additional manuscripts focusing on the secondary outcomes of the InCoPE-App will be prepared and submitted for publication in peer-reviewed journals. Upon completion of the study and after publication of the primary manuscript, all anonymized and summarized data can be requested from the researchers at the Institute of Sports and Sports Science of the Karlsruhe Institute of Technology, Germany.

The InCoPE-App will be evaluated in this study with respect to usability and effectiveness. After this evaluation, the participating nursing homes are allowed to further use the app to train their residents with dementia. Based on this, a dissemination plan will be developed to provide more nursing homes with the app, which is highly relevant in 2 ways. First, the continuing pandemic requires nursing assistants and residents with dementia to abide by strict hygiene measures, which is difficult when conducting a group-based exercise program possibly delivered by external employees such as trainers or instructors. Second, apart from pandemic circumstances, individualized group exercise programs in nursing homes are often delivered by nursing assistants who are not sufficiently trained for this purpose. Thus, the overall effect of exercise programs in nursing home settings is often limited. The InCoPE-App addresses this gap as it enables nursing assistants to deliver a scientifically based and individually assigned exercise program to people with dementia without requiring exercise science expertise or excessive prior training. Implementing the app in a nursing home setting may also be associated with economic advantages as additional employees with exercise science background to carry out a dementia-specific individualized exercise program may not need to be hired. One can conclude that the additional temporal expense might be balanced and the benefit of each participant can outweigh the expenses. The exact time and personnel resources required for implementation of the InCoPE-App will be assessed in the context of this study. This information can be used as key data to establish the InCoPE-App in other nursing homes.

Conclusion

The InCoPE-App is a novel, innovative, tablet-based intervention that allows nursing assistants to individually test and train people with dementia with regard to physical and cognitive capacities while meeting the hygiene and safety measures in place during the current COVID-19 pandemic. The InCoPE-App can be used by nursing assistants without prior exercise experience as it provides low-threshold testing procedures and implementation of an exercise program without the need for expert knowledge. This fact is also relevant in times after the pandemic constraints, because supplementation of the traditional treatments with the best possible physical exercise program is always challenging for nursing assistants who do not have the special training to deliver an individualized exercise program. The InCoPE-App will allow nursing assistants to regularly test the physical and cognitive performance of each individual and to subsequently train people with dementia on that basis. To the best of our knowledge, there is currently no app available that applies a similar approach in a nursing home setting. The InCoPE app is expected to provide nursing assistants a means to provide their residents with dementia a usable and feasible individualized exercise program that may increase physical and cognitive performance as well as quality of life. This may in turn have a positive impact on disease progression and nursing care.

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Authors' Contributions

All authors were members of the research team and participated in the design and preparation of the study. All authors contributed to the conception and design of the study. JB and BBF prepared the proposal to the ethics committee. JB, AS, and BBF supported the app development. All authors were involved in planning the manuscript. BBF wrote the manuscript. JB, AS, ST, JKR, and AW critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-meter walk test
CG: control group
CST: chair stand test
FES-I: Falls Efficacy Scale International Version
FICSIT-4: Frailty and Injuries: Cooperative Studies of Intervention Techniques-subtest 4
IG: intervention group
InCoPE: Individualized Cognitive and Physical Exercise
MMSE: Mini-Mental State Examination
PSSUQ: Post-Study System Usability Questionnaire
QOL-AD: Quality of Life–Alzheimer's Disease
TUG: Timed Up & Go

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Protocol

Developing an Anxiety Screening Tool for Children in South Africa: Protocol for a Mixed Methods Study

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Abstract

Background: Early childhood experiences such as trauma, exposure to violence, and poverty can significantly contribute to childhood anxiety, which is viewed as the most common mental health issue among children. In South Africa, there is no uniform tool to screen for anxiety during early childhood. This study aims to develop a tool to screen for anxiety in children aged 4 to 8 years, which could be utilized by preschool and foundation phase teachers to aid in the early identification of childhood anxiety.

Objective: The overall objective of this study is to explore understanding and perceptions of childhood anxiety among teachers, parents, and experts and to develop a tool to screen for anxiety in children aged 4 to 8 years.

Methods: This project will use a mixed method design that will consist of 4 stages. Stage 1 will consist of a scoping review. In Stage 2, data will be collected via semistructured interviews with 60 participants, including parents, teachers, and experts, and will be thematically analyzed. Stage 3 will consist of 20 experts and the researcher collaboratively formulating the proposed screening tool in the form of an e-Delphi component. Once the tool is refined, it will be piloted in Stage 4 with 20 teachers, and data will be analyzed with the Shapiro-Wilk test to test for normality. Additionally, factor analysis will be done to refine and restructure the tool as necessary.

Results: This project was funded from April 2020 to December 2021. Data collection began in September 2022 and is projected to conclude in December 2022 for the qualitative component. The e-Delphi component is expected to be carried out from March to November 2023. Ethical approval was obtained from the Biomedical Research Ethics Committee in November 2021.

Conclusions: Anxiety in early childhood has been linked to various repercussions in adolescence and adulthood, such as school dropout, substance abuse, anxiety disorders, depression, and suicide ideation. Therefore, identifying the presence of anxiety earlier on and providing the necessary referral services could aid in reducing the negative consequences of unidentified and untreated anxiety in early childhood.

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KEYWORDS

South Africa; mental health; anxiety; anxiety screening tool; screening; assessment; early childhood development; child; parent; primary caregiver; teacher; preschool; foundation phase; children; school; youth; development; perception

Introduction

Early childhood development (ECD) and childhood mental health have received substantial attention since being included in the United Nations Sustainable Development Goals (SDGs) [1]. Across the developmental lifespan, early childhood is the most important developmental phase as it includes and significantly influences the physical, socioemotional, mental, language, and cognitive spheres of development [2]. Therefore, ensuring a healthy early childhood could facilitate the overall development, well-being, and mental health of a child across their lifespan.

In early childhood, mental health is defined as a child's ability to develop close and secure relationships; to experience, manage, and express a full range of emotions, such as happiness, sadness, frustration, and discomfort; and to explore their environment and learn [3,4]. Mental health problems, which can occur as early as infancy, have been linked to childcare challenges and difficulty in preschool settings, including behavioral problems in school and difficulty learning and engaging with peers and educational content [5]. Anxiety has specifically been identified as the most common mental health challenge in early childhood [3], affecting the child's social interactions and ability to adequately express emotion. For instance, anxiety can interfere with a child's ability to transition from a home setting to a school setting. This can result in them displaying aggressive behavior when upset. Although anxiety is a normal response to stressful events [6], when experienced excessively, it results in significant distress and functional impairment [7]. However, there is no universal age-appropriate developmental description of how anxiety presents itself in children, thus contributing to prevalent study findings that suggest few children meet the criteria for anxiety as set out by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) [8]. Therefore, it is important to highlight and understand factors contributing to anxiety in ECD to identify how childhood anxiety manifests earlier.

Unrecognized and untreated anxiety symptoms in ECD have the potential to influence the way children interact with their peers, family, and community members [9,10]. Additionally, anxiety symptoms could persist and become more severe, placing children at risk for academic difficulties and school dropout [9,11] as well as the development of anxiety disorders and depression, suicide ideation, unemployment, and substance use disorders later in life [12,13]. However, there is a paucity of literature exploring anxiety during early childhood within the South African context.

To this end, research has found that about half of adults diagnosed with an anxiety disorder had an age of onset before 11 years [9,14], with 50% of cases showing symptoms before 6 years of age [15]. This indicates that anxiety symptoms can be present as early as the ECD phase. Within the South African context, a study conducted by Howard et al [16] found that preschool children (aged 2 to 6 years) showed elevated levels of anxiety symptoms and anxiety proneness compared to children in the Northern Hemisphere. Furthermore, earlier research in the Western Cape, South Africa, found that there was a prevalence between 22% and 25.6% for childhood anxiety symptoms among a sample of 7- to 13-year-olds [17]. This confirms that children in South Africa experience increased levels of anxiety [16]. Therefore, addressing anxiety in ECD is crucial to realizing the 2030 SDGs, specifically Goal 3, which is to ensure healthy lives and promote well-being across all developmental stages.

Significant importance should be placed on identifying anxiety symptoms in young children, which may have a powerful effect on their life trajectories. For example, screening for anxiety early could reduce anxiety-related consequences and improve life-course outcomes by facilitating necessary referrals and treatments. There is a growing body of evidence on educational settings being the most ideal for early intervention. According to Berger et al [18], Yatham et al [19], and Brown et al [20], school is a convenient setting for interventions to take place as it provides the space and opportunity to identify any mental health–related problems, especially for those who are unable to access traditional clinic-based mental health services. Additionally, providing intervention during the early childhood phase has been identified as the most promising and consequential [21]. This may also be related to the substantial amount of time children spend at school and the fundamental role it plays in child development [22]. As such, it would be ideal to screen for anxiety during early childhood within the preschool and foundation phase setting, as it will allow for the early identification of childhood anxiety.

Various international tools have been developed to measure anxiety levels in young children and adolescents. However, the most frequently used tools include the Screen for Anxiety-Related Disorders (SCARED) [23], Spence Children's Anxiety Scale (SCAS) [24], and the Preschool Anxiety Scale (PAS) [25]. SCARED and SCAS both consist of a child self-report and parent report, whereas the PAS consists of a parent and teacher report. These tools were developed to assess the intensity of anxiety symptoms specifically related to generalized anxiety disorder, separation anxiety disorder, panic disorder, social phobia, and school phobia [22]. SCAS additionally screens for fear of injury and obsessive compulsive disorder [22,26]. The SCARED questionnaire was developed "based on anxiety symptoms in clinical populations" for children 8 to 18 years [27], while SCAS measures anxiety symptoms in children aged 8 to 12 years. Additionally, PAS was developed for children aged 3 to 6 years to assist in clinical assessments and determine whether children are showing higher levels of anxiety [28-30]. Although these tools check anxiety levels in children, there is no tool to screen for the possible presence of anxiety in young children within the unique cultural context of South Africa.

Various cultures and belief systems are present in South Africa that can influence the way mental health is understood and treated. Therefore, understanding cultural influences on mental health can facilitate proper diagnosis and treatment [31]. A study by Booysen et al [32] found that participants understood and described mental illness symptoms in relation to their indigenous cultural perspectives. Thus, culture plays a key role in the conceptualization of how mental health is perceived and understood in South Africa. However, there is no literature that clearly indicates how different cultures in South Africa define anxiety and its symptoms. Therefore, with anxiety being the most common mental health issue in young children, it is imperative to consider the role culture plays in the way children express and experience anxiety as well as the way childhood anxiety is perceived by others. There is limited literature in South Africa that focuses on anxiety in early childhood [16,33,34]. A 2014 report revealed that Western Cape had a 12-month prevalence rate of 17% for mental disorders among children and adolescents [35]. This indicates that there is a significant number of children who have been diagnosed with at least 1 mental disorder within a 12-month period.

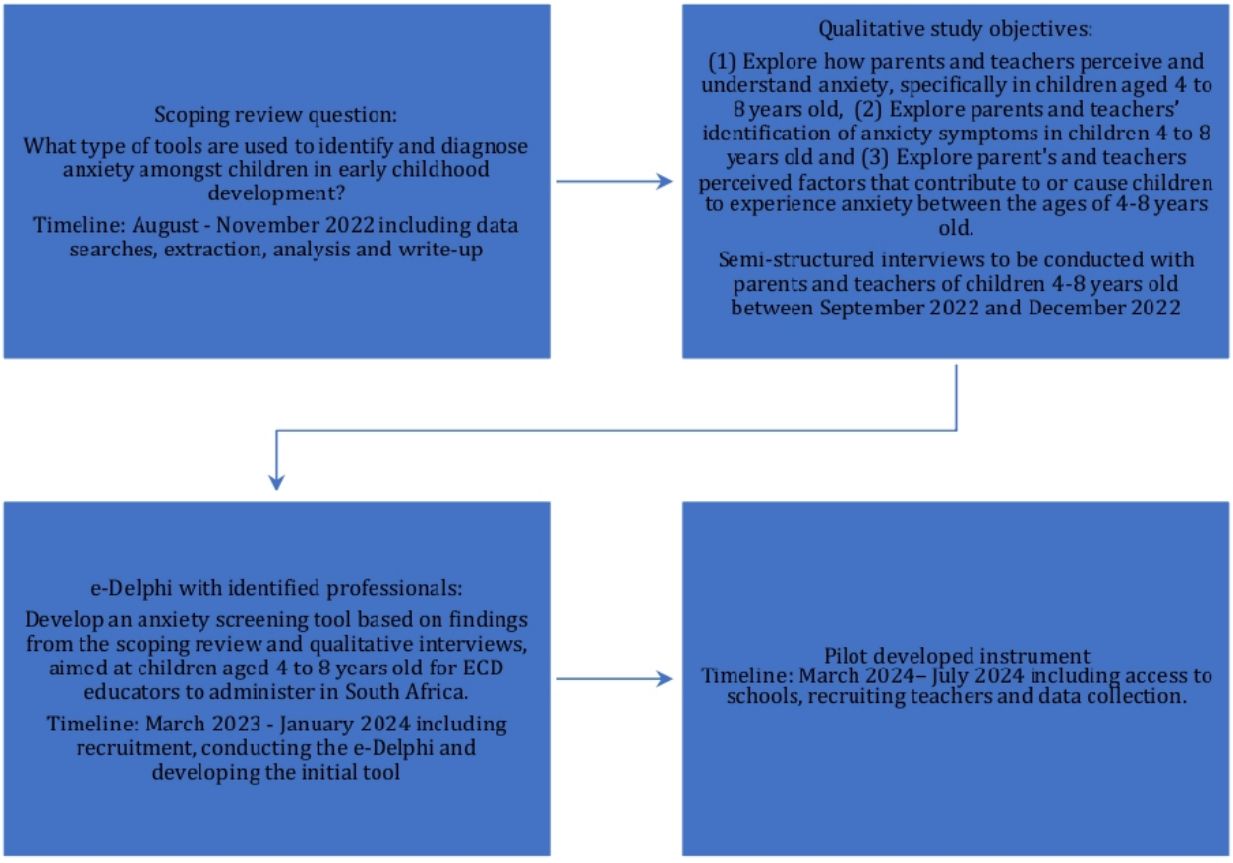
Although there are South African studies that have focused on the mental health of children [36,37] and the prevalence of childhood anxiety [38], the literature is scarce, dated, and does not specifically look at anxiety during early childhood. In addition, there is no appropriate tool within the country's multicultural and multilingual society to screen for the presence of anxiety in early childhood. This makes the availability of a suitable tool that takes cultural factors into account crucial to screen for the presence of anxiety during the ECD phase. Accordingly, this paper describes a process to develop a screening tool for anxiety in children aged 4 to 8 years within the South African context.

Methods

Research Design

This paper aims to outline a protocol for a 4-staged study based on an exploratory sequential mixed method design within a participatory framework. The exploratory sequential design is useful for developing new psychological tests or assessment instruments "based on an initial qualitative analysis and generalizing qualitative findings to a specific population" [39]. In addition, according to Creswell and Creswell [40], combining qualitative and quantitative data provides a deeper understanding of a phenomenon compared to using either approach individually [41]. The participatory action research (PAR) approach, which is a subset of action research, is characterized by participants working with researchers in a collaborative, self-inquiring, and systematic process [42]. It is a cyclical process that is used to explore participant concerns or issues that may impact their lives and aims to bring about meaningful change within communities [43]. The cyclical process includes "exploration, knowledge construction, and action at different moments throughout the research process" [43]. It is therefore applicable to this study, which aims to explore parents' and teachers' perceptions and understanding of anxiety and its contributing factors in children aged 4 to 8 years. The principal researcher (author FB) will work in collaboration with participants throughout the tool development process. This will inform and contribute to the development of an appropriate tool to screen for anxiety in children aged 4 to 8 years. Furthermore, it should be noted that parents and stakeholders (eg, teachers and experts) are the respondent groups throughout this research process and that children will not be directly involved. As shown in Figure 1, this research plans to conduct 4 sequential studies, referred to as Stage 1, Stage 2, Stage 3, and Stage 4, wherein the results of one study will guide the subsequent one.

Figure 1. Research process.



Stage 1: Identify Available Anxiety Screening Tools for Children Aged 4 to 8 Years

Stage 1 will comprise a scoping review to map the available anxiety screening tools for young children [43] and answer the following question: Which type of tools are used to identify and diagnose anxiety among children in early childhood development? The scoping review will be utilized to inform this study on various formats used for childhood anxiety instruments to identify different components of anxiety in children aged 4 to 8 years and to highlight its use, if any, within the South African context by considering both national and international peer-reviewed literature. This will aid in identifying the importance of a tool developed for circumstances unique to a country or context. Furthermore, this stage will be guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews) outline. Stage 1 will be used to further inform and strengthen the interview schedules in Stage 2.

Inclusion Criteria

Studies that include the use of anxiety screening tools specifically aimed at children will be eligible for inclusion in this review. Further inclusion criteria are studies that (1) include children between the ages of 4 to 8 and their parents, primary caregivers, or stakeholders; (2) are published in or translated to English; (3) peer-reviewed; and (4) use quantitative or mixed methods designs. The time frame will be open as there is little to no available literature in this field. Electronic searches will be conducted using databases such as Academic Search Complete, APA PsycArticles, CINAHL Plus, ERIC, and MEDLINE to search and retrieve literature. These databases were searched in August 2022, and the format of the search strategy differed depending on database requirements (where 1 database required the use of brackets to separate keywords in a search string while another did not). For example, when accessing Academic Search Complete, the following search strategy will be used: (1) childhood anxiety* AND tool OR scale; (2) childhood anxiety* AND instrument OR questionnaire; (3) anxiety in young children OR childhood anxiety* AND teacher scale OR teacher report OR teacher questionnaire; (4) Anxiety in young children OR childhood anxiety* AND parent scale OR parent report OR parent questionnaire; (5) Anxiety in the early years OR anxiety in young children OR anxiety in early childhood development* AND tool OR scale; (6) Anxiety in the early years OR anxiety in young children OR anxiety in early childhood development* AND instrument OR questionnaire; (7) Anxiety in the early years OR anxiety in early childhood development* AND teacher scale OR teacher report OR teacher questionnaire; and (8) Anxiety in the early years OR anxiety in early childhood development* AND parent scale OR parent report OR parent questionnaire.

Exclusion Criteria

Studies will be excluded if they are (1) not peer-reviewed, (2) not published or translated to English, (3) include children over the age of 8, and (3) do not use an anxiety scale/questionnaire. Qualitative-only studies and reviews will be excluded because this scoping review aims to map available tools to screen for anxiety in children aged 4 to 8 years.

Data Extraction and Analysis

A data extraction tool adapted from Arksey and O'Malley [44] will be used to organize information according to author, year of publication, country of origin, aims and purpose of the study, study population and sample size, methods, and key findings related to the scoping review question.

Stage 2: Identify and Describe Underlying Behaviors of Childhood Anxiety

This stage aims to establish local relevance and operational definitions of childhood anxiety. This will be done by exploring the different experiences, understanding, and perceptions of childhood anxiety from participants. The outcomes will then be used to assist in the development of the proposed tool in terms of language, concepts, and the cultural applicability.

Participants

Participants will be purposively sampled based on the following inclusion criteria to ensure they are appropriate for this study across different stages: (1) parents and caregivers 18 years of age or older (both parents or single parents and caregivers) who have at least 1 child between 4 and 8 years old; (2) teachers (preschool and foundation phase) who actively work with children aged 4 to 8 years; (3) identified experts in childhood anxiety and ECD, including researchers who are well published in the field, psychologists, and social workers; and (3) those who speak English, Afrikaans, or isiXhosa. Parents and stakeholders (teachers and experts) will be included in the qualitative data collection process to obtain a more holistic perspective on childhood anxiety.

Data Collection Tool

Semistructured interviews will be used to explore the perceptions of parents and primary caregivers and stakeholders. The interview schedule will consist of 2 parts: (1) demographic information and (2) questions broadly relating to parents' and stakeholders' perceptions of childhood anxiety. Interviews with parents will be conducted using interview schedule 1 (Multimedia Appendix 1), and stakeholder interviews will be conducted using interview schedule 2 (Multimedia Appendix 2). These interviews will be guided by the theory, literature, and context and will be conducted in English, Afrikaans, or isiXhosa, as these are the prominent languages spoken in the Western Cape of South Africa [45]. Interviews will be carried out with help from research assistants who are fluent in at least 2 languages, including English. The interview schedule will be piloted with approximately 3 parents and 3 stakeholders to ensure that the questions are easily understood. All interviews are estimated to last between 45 to 60 minutes, and permission will be sought for interviews to be audio recorded.

Data Collection

Approximately 60 participants (5 parents and primary caregivers, 3 teachers, and 2 experts from each district in the Western Cape) will be recruited for individual interviews. According to Morse [46], the sample size relatively depends on the quality of the data, with a maximum of 30 to 60 participants being appropriate. However, data collection will cease once saturation is reached. Sampling strategies for parents and

primary caregivers will include door-to-door recruitment, snowball sampling, ECD centers, and schools. All COVID-19 safety protocols will be strictly adhered to. These include maintaining a safe social distance during interviews, wearing a mask, and using hand sanitizer before and after the in-person interview. In addition, online platforms such as Facebook, Instagram, and WhatsApp will be used to recruit participants. Similarly, teachers will be accessed through schools, including preschools and ECD centers.

Data Analysis

Once data collection is completed and all interviews are transcribed and translated (where necessary), data will be analyzed thematically [47]. Specifically, data will be familiarized by reading and rereading transcriptions, after which initial codes will be generated. Themes will then be searched by sorting the different codes into ideas that are related. Themes will then be identified and named to ensure that meanings are captured and definitions for each theme are generated adequately. Once themes are described and defined, quotations from transcripts will be used to illustrate and capture the essence of the identified themes.

Stage 3: Develop Initial Instrument

The aim of this stage is to develop a tool to screen for anxiety in children aged 4 to 8 years with the assistance of a professional panel that has knowledge of and experience with anxiety and early childhood. Information gathered from Stages 1 and 2 will also be used to conceptualize childhood anxiety and identify and describe the behaviors that underlie anxiety in children aged 4 to 8 years. In collaboration with the panel, a pool of initial items that reflects the purpose of the screening tool will be generated [48]. Therefore, a Delphi study will be conducted on the panel to facilitate the development of the tool, sequence its items and supporting material, determine the format of the measurement [48,49], and provide feedback on generated items to ensure cultural sensitivity [50]. As such, the cyclical process of PAR will aid in gathering the necessary information to achieve the aim of Stage 3.

Participants

Approximately 20 participants will be included in the Delphi study. This includes research psychologists, clinical and school psychologists, or social workers, as well as anyone who has published scientific research related to anxiety and/or early childhood within the South African context. Participants will be purposively selected according to the following criteria: (1) have knowledge of and experience with the topic; (2) are willing to participate; (3) have the time to participate; (4) have effective communication skills [51]; and (5) have least 5 years of experience in the field and are registered with respective professional councils. These criteria will ensure the selection of participants who are experts in the field.

Data Collection

An e-Delphi technique will be employed to inform the development of initial items for the tool to screen for anxiety in children aged 4 to 8 years. This online technique will be used for participants to collaboratively engage in the formulation of the proposed screening tool and to review the tool in its entirety. The e-Delphi will consist of online engagements using discussion forums via Google Chat. The participating experts will be asked to discuss the components of anxiety and specify how it may present in early childhood. Following this, initial items will be generated and assessed. Based on the discussions and expert opinions, the principal researcher (author FB) will draft the proposed screening tool and forward it to the panel of experts for review. At this stage, participants will be requested to read each item and comment on its clarity, aesthetics, relevancy, tone, length of time it takes to respond to the item, and cultural sensitivity [50]. The purpose of this is to test for face validity, item validity, sampling validity, outcome validity, and generalizability [50]. This step will be complete once the questions are answered, a consensus is reached, saturation is achieved, or satisfactory information has been exchanged [52]. In the case that participants believe the instrument to be underdeveloped, the principal researcher will go back to the discussion forum and request further assistance from the expert panel on how to improve the screening tool.

Data Analysis

Based on participant responses to the open-ended questions accompanying each item on the developed instrument, an inductive thematic analysis will be carried out to analyze the data according to the procedures outlined by Clarke and Braun [47,53].

Stage 4: Pilot Initial Instrument

In Stage 4, the instrument developed in the previous stage will be tested in a pilot study to determine its validity, reliability, and consistency.

Participants

A pilot study will be conducted with preschool and foundation phase teachers to test the screening tool for anxiety in children aged 4 to 8 years. Participants will be purposively selected from ECD centers, preschools, and schools, and teachers in the foundation phase will be specifically targeted. The pilot will be conducted to test the developed quantitative tool in the field and restructure where necessary. Participants will be requested to complete the developed tool to screen for anxiety in children aged 4 to 8 years either in person or online.

Sampling

Stratified random sampling will be used in this stage to ensure that the sample is representative of the teacher population, for whom the tool to screen for anxiety in children aged 4 to 8 years is aimed. According to 2016 education statistics in South Africa [54], the Western Cape has approximately 37,518 teachers; therefore, the preliminary sample size of the respondent group is estimated to be 400, rounded off from 395.780, based on the Yamane formula. However, the sample size is subject to change as it is recommended to have an adequate case-to-variable ratio from 5 to 10 participants per item [50]. That said, approximately 67 teachers will be recruited from each of the 6 districts in the Western Cape.

Data Collection

Teachers will be requested to use the developed tool to screen for anxiety in children aged 4 to 8 years by considering at least

1 child in their classroom. This will be done to test for item validity, concurrent and predictive validity (criterion-related validity), structure, convergent, discriminant, and divergent validity (construct-related validity), and internal consistency of the scale. In addition, ethical, practical, and cultural issues related to the instrument will be assessed [55] to avoid items inadequately depicting acceptable internal consistency. However, before teachers can complete the developed tool with the consideration of at least 1 child, they will request and receive the consent of both the parent and the child. Once the instrument is completed by participants, it will be entered into SPSS.28 (IBM Corp) software.

Data Analysis

Once data collected from the pilot study is captured and cleaned in SPSS.28, test reliability will be conducted to establish internal consistency and to test the assumptions for multivariate statistical analysis. This will be done by conducting a Shapiro-Wilk statistical analysis to test for normality. Item-scale correlations will be used to assess criterion- and construct-related validity and determine how items correlate with each other on the scale. In addition, the Bartlett test of sphericity will be conducted to determine the homogeneity of variance; this tool is recommended to be used before conducting a factor analysis to determine if there is redundancy between identified variables [56]. Additionally, a Kaizer-Meyer-Olkin test will be conducted to determine sample adequacy and the confidence level of the factors in the developed instrument. Based on those findings, a prevalence test will be done, and structural validity will be assessed through exploratory factor analysis to determine the structure of the measure and examine the internal validity of the screening tool. Based on the results, problematic items will be refined or discarded.

Ethics Approval

Ethical approval (BM21/9/12) was obtained from the Biomedical Research Ethics Committee at the University of the Western Cape. The purpose of the study and its details will be explained to prospective participants, and those who wish to take part will be asked to provide consent before undergoing an interview. Participants will be informed of their right to withdraw from the study at any time without consequence and will be assured that their contribution is completely anonymous. Confidentiality will be ensured by participant names being replaced with pseudonyms or codes. If a participant's preferred language is isiXhosa, permission will be requested for a research assistant to sit in on the interview for translation purposes. Additionally, audio-recorded files, transcriptions, and raw quantitative data will be password protected and accessible by only the researcher and supervisors. Data will be disposed of by shredding after 5 years. Furthermore, to minimize any potential risk to participants, such as discomfort and psychological or emotional harm, they will be provided with the contact details of relevant referral services, including Families South Africa, Department of Social Development, and Childline. In addition, the principal researcher will gather the telephone number of organizations in areas that offer free counseling services and give them to participants. Furthermore, all COVID-19-related rules and regulations set out by the South African government will be strictly adhered to, such as wearing masks, sanitizing hands, and maintaining social distance. COVID-19 restrictions may affect in-person data collection; therefore, where applicable and feasible, interviews will be conducted via online platforms or telephone. In the case that any participant presents with COVID-19 symptoms, data collection will be ceased to ensure the safety of the participant and researcher. Any disclosure of COVID-19 cases will be treated as confidential. Participants who request further information or assistance related to COVID-19 will be referred to their nearest clinic.

Results

The project was funded from April 2020 to December 2021. The data collection dates are projected as follows. The scoping review search and screening process began in August 2022, with an expected completion date of November 2022. Qualitative data collection began in September 2022 and is expected to be done by December 2022 and will include recruitment, data collection, and analysis. The qualitative data analysis write-up in preparation for the e-Delphi component is projected to start in March 2023. Furthermore, in collaboration with the e-Delphi participants, who will be recruited in March 2023, the initial tool to screen for anxiety in children aged 4 to 8 years will be formulated between November 2023 and January 2024. The pilot study will take place between March and July 2024 depending on access provided and the availability of schools and teachers. Results are expected to be published in 2024.

Discussion

Expected Findings

This study anticipates the identification of available tools to screen for anxiety in young children, specifical children between the ages of 4 and 8. This will be done by conducting a scoping review of peer-reviewed studies that have developed and/or used an anxiety tool for young children. Additionally, the qualitative component of this study will highlight common understanding and perceptions of early childhood anxiety, internal and external factors contributing to anxiety in early childhood, and behaviors associated with anxiety during early childhood. The qualitative component will also consider cultural roles specific to the South African context. The e-Delphi component is anticipated to include experts in early childhood or anxiety to provide professional views and experiences. This will ensure that a holistic perspective is considered in the development of the anxiety screening tool.

Anxiety originating in childhood has been associated with greater severity and comorbidity as opposed to anxiety originating during adulthood [57], and it has been linked to various consequences in adolescence and adulthood, such as school dropout, substance abuse, anxiety disorders, depression, and suicide ideation. Parental psychological control has been identified as a contributing factor, in that parents may transmit anxiety-related fear to their children through verbal communication and overcontrol (eg, telling a child that certain things will scare them or that if they climb too high or run too fast, they will get hurt). Percy et al [57] indicate this by

highlighting that the ways in which parents communicate with their young children, both implicitly and explicitly, can increase a child's anxious behaviors and beliefs. Additionally, other factors have been identified in the etiology of childhood anxiety. These include, but are not limited to, a child's temperament, maternal psychopathology, family conflict, parenting style, child neglect and abuse, lack of close adult relationships, bullying, rejection, and starting at a new school [58,59]. These factors point to the importance of including childhood mental health in policy and ensuring the accurate execution of interventions.

South Africa is considered to be advanced in developing and implementing health and social policies in comparison to other lower- and middle-income countries. However, a policy analysis by Mokitimi et al [60] revealed that no South African province had a child and adolescent mental health (CAMH) policy or implementation plan to support the National Mental Health Policy Framework and Strategic Plan 2013-2020. This suggests that although a national CAMH policy exists, there is poor implementation across all 9 provinces, pointing to the relevance of this study, which could aid policy making because developing a tool to screen for anxiety in ECD could provide data on CAMH in South Africa. Although there are numerous tools to assess the levels of childhood anxiety and screen for anxiety-related disorders, it is unclear whether a tool already exists to evaluate the possible presence of anxiety in children aged 4 to 8 years, specifically within the South African context.

Limitations

An identified limitation of this project is that the tool is not aimed to be directly administered to child respondents. However, the proposed screening tool is aimed to be administered by a teacher to determine whether a child shows any signs of anxiety to facilitate early identification and treatment. Another limitation is that this project is not a longitudinal study; therefore, the effectiveness of the tool cannot be monitored over a longer time period.

Conclusion

Addressing anxiety in ECD is crucial in realizing the 2030 SDGs, specifically Goal 3, which is to ensure healthy lives and promote well-being across all developmental stages. Accordingly, the findings of this study can significantly contribute to the growing body of South African literature on anxiety in ECD, and the developed tool can assist in the early identification of childhood anxiety and provide referrals for treatment. Research findings will be disseminated in the form of a dissertation, scientific publications, and conference presentations. Findings will be presented to participants in the form of a verbal presentation or infographics before the tool is disseminated.

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Authors' Contributions

FB, ER, and NVR conceived and conceptualized the study and the paper. FB designed and wrote the first draft of the manuscript. BOA, ER, and NVR contributed to the development of the paper and provided comments for improvement. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Parents and primary caregiver English interview schedule.
[DOCX File , 21 KB - resprot_v11i9e37364_app1.docx]

Multimedia Appendix 2
Stakeholders English interview schedule.
[DOCX File , 16 KB - resprot_v11i9e37364_app2.docx]

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Abbreviations

CAMH: child and adolescent mental health
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECD: early childhood development
PAR: participatory action research
PAS: Preschool Anxiety Scale
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews
SCARED: Screen for Anxiety-Related Disorders
SCAS: Spence Children's Anxiety Scale
SDG: Sustainable Development Goal

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Protocol

Using Normative Language When Describing Scientific Findings: Protocol for a Randomized Controlled Trial of Effects on Trust and Credibility

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Abstract

Background: Trust in science and scientists has received renewed attention because of the "infodemic" occurring alongside COVID-19. A robust evidence basis shows that such trust is associated with belief in misinformation and willingness to engage in public and personal health behaviors. At the same time, trust and the associated construct of credibility are complex meta-cognitive concepts that often are oversimplified in quantitative research. The discussion of research often includes both normative language (what one ought to do based on a study's findings) and cognitive language (what a study found), but these types of claims are very different, since normative claims make assumptions about people's interests. Thus, this paper presents a protocol for a large randomized controlled trial to experimentally test whether some of the variability in trust in science and scientists and perceived message credibility is attributable to the use of normative language when sharing study findings in contrast to the use of cognitive language alone.

Objective: The objective of this trial will be to examine if reading normative and cognitive claims about a scientific study, compared to cognitive claims alone, results in lower trust in science and scientists as well as lower perceived credibility of the scientist who conducted the study, perceived credibility of the research, trust in the scientific information on the post, and trust in scientific information coming from the author of the post.

Methods: We will conduct a randomized controlled trial consisting of 2 parallel groups and a 1:1 allocation ratio. A sample of 1500 adults aged ≥18 years who represent the overall US population distribution by gender, race/ethnicity, and age will randomly be assigned to either an "intervention" arm (normative and cognitive claims) or a control arm (cognitive claims alone). In each arm, participants will view and verify their understanding of an ecologically valid claim or set of claims (ie, from a highly cited, published research study) designed to look like a social media post. Outcomes will be trust in science and scientists, the perceived credibility of the scientist who conducted the study, the perceived credibility of the research, trust in the scientific information on the post, and trust in scientific information coming from the author of the post. Analyses will incorporate 9 covariates.

Results: This study will be conducted without using any external funding mechanisms.

Conclusions: If there is a measurable effect attributable to the inclusion of normative language when writing about scientific findings, it should generate discussion about how such findings are presented and disseminated.

Trial Registration: Open Science Framework n7yfc; https://osf.io/n7yfc

International Registered Report Identifier (IRRID): PRR1-10.2196/41747

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KEYWORDS

trust; trust in science; scientific communication; meta-science; RCT; randomized controlled trial; infodemic; COVID-19; misinformation; normative language; meta-cognitive; cognitive; scientific information; credible; credibility

Introduction

Trust in Science and Scientists

The "infodemic" [1] accompanying the COVID-19 pandemic [2,3] has reinforced the importance of studying how people perceive information about and from scientific studies. When people are presented with a high volume of information of varying accuracy, we propose that there exists a broad social interest in *people making decisions based on the best available evidence*. Our team's epistemological framework is that the scientific method is an excellent means of producing evidence. However, the suitability of the scientific method for producing knowledge, in general, does not necessarily mean that all purported scientific findings are of equal weight or that all scientists' findings or statements are trustworthy [4,5]. Indeed, alongside truly remarkable scientific discoveries during the pandemic, Retraction Watch recently documented its 250th COVID-19 paper retraction, and many of the papers on their list are associated with commonly shared misinformation about the pandemic (eg, the supposed role of 5G networks in spreading COVID-19) [6]. Thus, although we will shortly argue that trust in science and scientists is valuable to understand, it is important not to conflate such trust with a more simplified aphorism such as "trust the science" [7], which (in our view, inappropriately) implies a singular "science" that is inherently worthy of trust.

At the same time, even though trust is defined and measured in a variety of different ways, studies conducted across multiple different populations have identified associations between trust in science and intention to get vaccinated or boosted for COVID-19 [8-12], as well as adherence to other measures to mitigate harm from the pandemic (eg, nonpharmaceutical interventions) [13-17]. Thus, even if the exact nature of the relationship is unclear, it is reasonable to speculate that trust in science and scientists is associated with people's behaviors during a public health emergency such as COVID-19. We also note that trust in science and scientists is associated with belief in misinformation. Our research team has been studying trust in science and scientists as a complex and multifaceted variable using a conceptualization from Nadelson et al [18]. They validated a 21-item measure that includes multiple conceptual domains related to trust, computed using responses to items such as "We cannot trust scientists to consider ideas that contradict their own," and "When scientists form a hypothesis they are just guessing" [18]. Using their 21-item measure to compute an aggregated value for trust, we found evidence of strong associations between low trust in science and belief in scientifically unsupported statements (eg, "misinformation") about COVID-19 [19,20] and opioid overdose and naloxone [21].

We used those findings to develop a digital intervention, very deliberately rejecting approaches focused on the manipulation of trust in favor of creating truthful informational infographics to explain common misperceptions about science (ie, why it is appropriate for scientists to change their minds in response to new evidence) [22]. In a large preregistered, randomized controlled trial, we found evidence that 60 seconds of exposure to one such infographic, which featured an example of changing recommendations around butter and margarine, slightly and significantly increased trust in science and scientists and slightly reduced the likelihood that participants whose trust was thereby increased would endorse COVID-19 misinformation (ie, a mediational, but not direct, intervention effect) [20]. However, we observed no effects on behavioral intentions whatsoever, even though exploratory analyses showed that the trust variable remained associated with behavioral intentions [20].

This difference between the intervention's effects on beliefs and behavioral intentions may raise questions about the ways in which scientific claims, as well as misinformation, may contain both cognitive and normative elements (which we unpack subsequently) and whether such elements are associated with trust in science and scientists. Furthermore, recent papers have reemphasized the importance of attending to both universals (eg, "trust in science and scientists") and particulars (eg, "credibility of a specific scientist or claim") in this area of study [4,5]. Thus, the remainder of this introduction makes the case for rigorously examining a seemingly small—but potentially important—distinction between cognitive and normative claims and the impact of such a difference on universal and particularized trust and describes our plan to do so.

Cognitive and Normative Scientific Claims

In this study, we will scrutinize the differences between "cognitive" (ie, epistemic) claims of scientific findings and "normative" claims (ie, recommendations). For many scientific endeavors (such as experiments or evaluative studies), a key outcome of the research is 1 or more cognitive claims. A basic example of a cognitive claim is "the current is really strong out by the pier," which is an assertion about the strength of the current. Importantly, a cognitive claim does not include a recommendation about what we ought to do if the claim is true. Such "ought" statements are instead normative claims, which pertain to what a person *should do* (eg, if it is the case that the current is really strong out by the pier, "...you should not swim there") [23].

In a consequentialist account of rationality, cognitive claims can be separated from normative or practical claims [23]. We often use others' cognitive claims to understand the world around us (eg, "we know by trusting what others tell us") [24]. This trust is necessary because no person has the ability to generate empirical knowledge about everything (given constraints such as capacity, resources, interest, and time). Thus, people frequently make decisions about which and whose cognitive claims to trust [25].

In contrast, normative claims presume a framework of interests (eg, not wanting to swim in dangerous places), but such framing may not always apply to all persons (eg, someone who is at the pier to test a device built to measure current strength). Even if we trust a cognitive claim, we may not trust an associated recommendation [26]. A helpful real-life anecdote can be found in a headline from July 2021 titled "People are dressing in disguise for COVID-19 vaccines, Missouri doctor says" [27]. For the people in that story, the recommendation to get vaccinated was complicated, not because of any explicit disbelief in scientific cognitive claims about the vaccine, but because it did not account for a strong competing interest in not being "ridiculed" by friends, family, or coworkers. Similarly, when physical conflicts—including some resulting in death—erupted across the United States in 2021 over face masks, media coverage suggests the primary concern was not the science behind face masks, per se, but rather whether people *should* or *should not* be wearing them in a particular public space and time [28-31].

We hypothesize that some meaningful percentage of variability in trust in science and scientists, both generally and at the level of specific claims and persons, is attributable to the linguistic entanglement of cognitive and normative claims (eg, in press releases, popular summaries, and social media). In particular, we expect that some portion of mistrust is unrelated to scientific epistemic claims and may instead be explained by perceptions of discordant interests between laypersons and scientists. If that is the case, then we would expect to see reduced levels of trust and perceived credibility in study participants exposed to both a cognitive and normative claim about a study compared to those exposed only to a cognitive claim (ie, "I believe your finding, but I don't agree with your recommendation"). If we are correct, it may have important ramifications for the way in which scientific findings are reported at multiple levels (eg, abstract, press release, news coverage, and social media).

Study Objectives and Hypotheses

Our study will draw conclusions by randomizing a large, nationally representative sample of US adults to view a sample social media post that either (1) shares a cognitive claim from a 2020 study on face masks (control group), or (2) shares the same cognitive claim but also includes a normative claim about what people should do, given the cognitive claim, which is also from that study (intervention group; see Methods). We hypothesize the following (see Table 1):

- Hypothesis 1: Overall trust in science and scientists (21-item scale) [18] will be significantly lower in the intervention arm (cognitive and normative claims) than the control arm (cognitive claim only).
- Hypotheses 2-5: The credibility of the scientist who conducted the study, credibility of the research, trust in the scientific information on the post, and trust in scientific information coming from the author of the post [32] will each be significantly lower in the intervention arm (cognitive and normative claims) than the control arm (cognitive claim only).
- Preregistered analyses (without hypotheses): We will study the interaction between the study arm and political orientation for each of the 5 preregistered hypotheses.

Table 1. Design table.

Question	Hypothesis (if applicable)	Sampling plan (eg, power analysis)	Analysis plan	Interpretation given to different outcomes
What is the effect of intervention arm assignment on overall trust in science and scientists (21-item scale)?	Overall trust in science and scientists (21-item scale) will be significantly lower in the intervention arm than the control arm.	With 80% power (2-tailed test), this sample will allow us to detect small effects at α=.05 (Cohen *d*=0.14) and at corrected α=.01 (Cohen *d*=0.18) for differences between groups.	ANCOVA[a], incorporating all 9 listed covariates	A significant effect will be interpreted as evidence that the inclusion of normative language caused the change (if the change exists), regardless of direction.
What is the effect of intervention arm assignment on the credibility of the research, credibility of the scientist who conducted the study, trust in scientific information from the author of the post, and trust in the scientific information on the post?	For hypotheses 2 through 5, each dependent variable will be significantly lower in the intervention arm than the control arm.	With 80% power (2-tailed test), this sample will allow us to detect very small effects at α=.05 (Cohen *d*=0.14) and at corrected α=.01 (Cohen *d*=0.18) for differences between groups.	ANCOVA, incorporating all 9 listed covariates	A significant effect will be interpreted as evidence that the inclusion of normative language caused the change (if the change exists), regardless of direction.
Are there any significant interactions between intervention arm assignment and political orientation on any of the prespecified dependent variables?	N/A[b]	N/A	Linear regression including the interaction between intervention arm and political orientation; the model will include the remaining 8 covariates	A significant interaction will be interpreted as possible evidence that political orientation may mediate or moderate the effect of including normative language in some way, regardless of direction, but that further research is needed.

[a]ANCOVA: analysis of covariance.

[b]N/A: not applicable.

Methods

Ethics Approval and Consent to Participate

This study will comply with relevant ethical regulations as outlined and approved by the Indiana University Institutional Review Board (16141) on August 2, 2022. Informed consent will be obtained from participants using electronic agreement to a study information sheet embedded at the beginning of the experiment. Participants will be paid US $1.50 on the successful completion of the study and submission for compensation (see Sampling Plan).

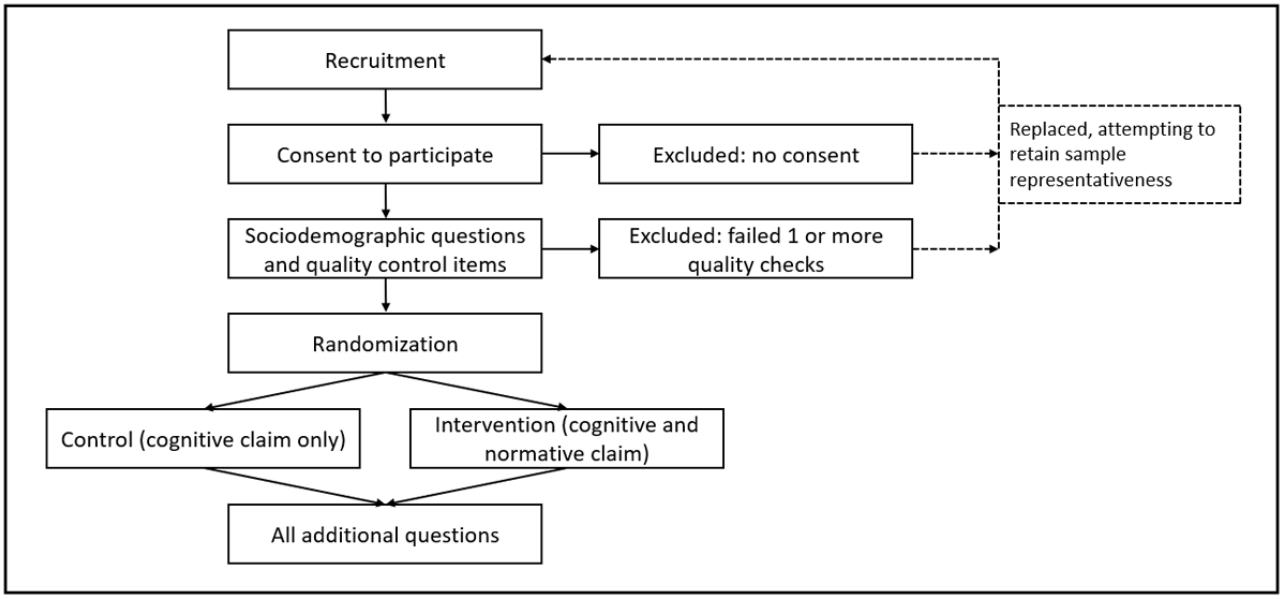
Design

Trial Design

We will conduct a randomized controlled trial consisting of 2 parallel groups and a 1:1 allocation ratio. Our planned study workflow is provided in Figure 1. Allocation will be automated by the Randomizer feature in the QualtricsXM platform [33] and thus, by definition, will be concealed from researchers until after each case has been assigned. However, we note that based on our prior experience, the use of data quality checks and the 2-step survey completion procedures in the Prolific platform can result in unbalanced allocation for a very small portion of the sample as recruitment approaches the planned limit (eg, if the number of usable surveys exceeds the number of surveys solicited, the excess surveys may not be allocated 1:1 but will still be included following sensitivity analysis) [20].

This study will be, in principle, a double-blind study; participants will be unaware that they are being randomized to a condition, and allocation will be done exclusively by software. However, analysts will not be blinded to the meaning of the group assignment variable.

Figure 1. Study design and workflow.



Participants and Procedures

This study will solicit participants (n=1500) from the Prolific crowdsourced US representative participant pool, which provides a cross-section of age, sex, and race/ethnicity that mirrors the national US population [34]. This sampling frame also provides the de facto eligibility criteria of being aged ≥18 years and residing in the United States. Studies have found the Prolific platform to produce high-quality research data in general and relative to competing services (eg, Qualtrics and Dynata panels, Amazon MTurk, and CloudResearch) [35,36].

When individuals indicate interest in participating in the study, they will be provided with a link to the experiment, which will be hosted on the QualtricsXM platform. Participants who agree to participate in the study (study information sheet) will complete the first block of questions, which will include sociodemographic items intermixed with screening questions to identify the risk of low-quality data (ie, virtual private network or bot use, inattention, and dishonesty) [37]. Individuals who fail 1 or more checks will be considered ineligible for the study and asked to return the study to the Prolific platform for reselection.

As noted in Figure 1, randomization will occur after all determinations of eligibility to preserve sample composition and allocation. The study will be fully insular (eg, all components occur within the QualtricsXM platform and within 1 "sitting"). To mitigate the potential impact of missing data, participants will not be permitted to advance the survey if they have not answered all questions on a given page. All data will be exported directly from the QualtricsXM platform to a local data file once the study closes, and the code used for data cleaning (see Sampling Plan) will be shared alongside the raw data.

Intervention and Control Description

To isolate the specific effects of normative language in describing scientific findings, we will show participants 1 of 2 fake social media posts depending on the study arm to which they are randomized. The posts will be identical except for the inclusion of normative language in the intervention post. To improve ecological validity [38], both posts will be designed using the formatting parameters for modern Facebook timeline posts as displayed in a web browser using "night" mode (see Figures 2 and 3). The posts will appear as posts "Suggested for you" from a generic science page, which is the primary subheading that Facebook uses when inserting content that is not explicitly followed on a person's timeline. The lead-in text will read, "Today's post highlights a study published back in April 2020, right after the COVID-19 pandemic arrived in the United States. This was from a peer-reviewed paper in *Infectious Disease Modeling*." Both posts will be accompanied by the same generic image of a surgical face mask and a bottle of hand sanitizer.

Additionally, in service of ecological validity, the written content of the graphics will be drawn directly from a highly cited April 2020 paper on face masks for the prospective prevention of COVID-19 [39]. The control post (Figure 2) will feature only a cognitive claim: "Scientists used models based on data from New York and Washington. Their results showed that 'broad adoption of even relatively ineffective face masks may meaningfully reduce community transmission of COVID-19 and decrease peak hospitalizations and deaths.'"

The intervention post (Figure 3) will include the same cognitive language but also add a normative statement derived from the same source paper. It will add "Based on their findings, the study authors suggested 'that face mask use should be as nearly universal (i.e., nation-wide) as possible and implemented without delay, even if most masks are homemade and of relatively low quality.'"

Figure 2. Control image.

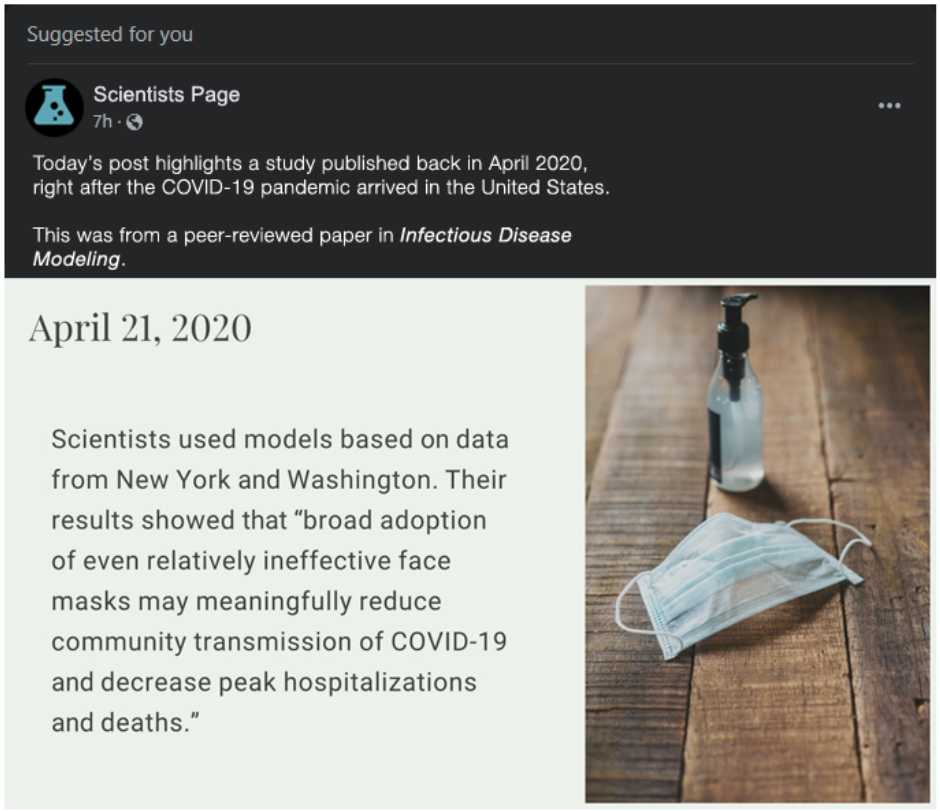
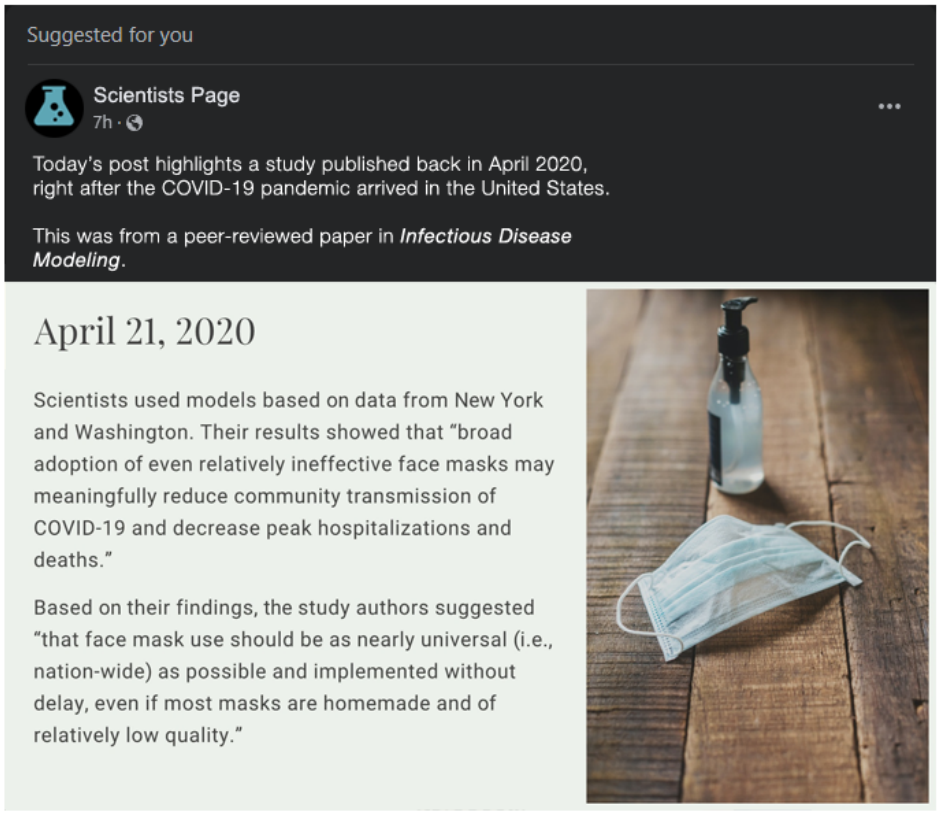


Figure 3. Intervention image.



Once the image is displayed, participants will not be able to advance the survey for at least 30 seconds (the button to continue the survey will be linked to a timer). A message indicating this delay will be provided on the screen. After participants advance, they will transition to a screen featuring a smaller copy of the image appropriate for their study arm, along with 1 (control) or 2 (intervention) comprehension questions.

- Both arms: (True/False) "In the social media post you read about a scientific study from April 2020, the study authors found that face masks could reduce the spread of COVID-19 as well as lowering hospitalizations and deaths."
- Intervention arm only: (True/False) "In the social media post you read about a scientific study from April 2020, the study authors recommended that everyone in the US should start wearing masks immediately."

Any response other than "True" for either question will display a message asking the participant to read the post carefully again, and then participants will be returned to the social media post (no 30-second delay on subsequent viewings), from which they can proceed forward to the comprehension questions again.

Sampling Plan

Sample Size Determination and Power Analysis

As previously described, we will recruit 1500 individuals from the Prolific platform, with equal allocation to study arms. This sample size is currently the largest number of people for which the Prolific platform can assure national representativeness. We made the decision to recruit a large number of participants because we were unable to locate any baseline studies with which to estimate effect size, so we wanted to be conservative. In addition, although the issue of face masks continues to be a point of public contention, the prevalence of public health mandates related to face masks is lower than those in 2020-2021, which we suspect may serve to suppress the effect size relative to what it would be in the midst of more active social discord focused on that topic. With 80% power (2-tailed test), this sample will allow us to detect small effects at α=.05 (Cohen d=0.14) and at corrected α=.01 (Cohen d=0.18) for differences of trust in science between treatment and control. In keeping with modern inferential statistical recommendations, we will report all P values precisely rather than by threshold [40] and provide a balanced interpretation, especially where .01<P<.05.

Technical Exclusion and Inclusion Procedures

With participant recruitment through a web-based pool, the number of usable responses is specified first (ie, the sample size)—in this case, 1500. When participants complete the survey, they will submit evidence of completion to the researchers, who will then approve payment via the Prolific platform. When an individual is rejected for payment (either at the time of submission for payment or at any other time), they will be resampled and replaced by a new member of the pool who matches their sociodemographic characteristics (eg, age, sex, and race/ethnicity). As a result, the number of participants who accept the survey initially will generally be different than the final sample size. This difference can occur for the following reasons (we provide *rough estimates* of prevalence based on a prior large study with the Prolific platform) [20]:

- Excluded: refusal to participate by declining consent (approximately 0.19%)
- Excluded: failing a quality control check and "returning" the survey (approximately 2.14%)
- Excluded: exiting the Qualtrics platform immediately after consenting to participate (approximately 0.37%)
- Excluded: exiting the Qualtrics platform prior to accessing the intervention, typically, but not always, after being informed of failing a quality control check (approximately 2.88%)
- Included: completing the full study correctly but failing to submit a request for payment (approximately 1.58%)

The overall estimated impact is that is roughly 5.57% of individuals who initially access the survey from the study pool will end up being rejected and resampled in the process of reaching the targeted sample size of 1500. Subsequently, a small number of individuals (roughly 1.58%) may fail to submit for payment but otherwise provide good data; these individuals will be analyzed in the arms to which they were assigned (but as noted earlier, will not be allocated 1:1).

Analysis Plan

Primary Outcomes

The primary outcomes are as follows.

- Hypothesis 1
  - Overall trust in science and scientists will be measured by the 21-item scale developed and validated by Nadelson et al [18]. An example item from the scale measures agreement with the statement, "When scientists change their mind about a scientific idea it diminishes my trust in their work." This scale has demonstrated excellent internal reliability in our previous studies with crowdsourced samples (α>.900) [19-22,41].
- Hypotheses 2 through 5
  - Single-item measures of credibility and trust that are specific to the hypothetical social media post and the scientist who conducted the study, from Song et al [32]
  - "How credible is the scientist who conducted the study described in the post?" (1=not credible at all to 7=extremely credible); note that this language is slightly different than the original item to avoid ambiguity arising from the potential that a scientist authored the social media post
  - "How credible is this research?" (1=not credible at all to 7=extremely credible)
  - "I would trust scientific information if I knew it came from this author." (1=strongly disagree to 7=strongly agree)
  - "I trust this scientific information." (1=strongly disagree to 7=strongly agree)

Covariates

The covariates are as follows.

- Familiarity with science will be measured by 1 item asking, "How often do you read science papers or science in the

news?" (1=never to 5=always) [32]; this item was suggested in Song et al [32] as being potentially important to consider
- Level of religious commitment (0=low to 10=high), as used in our previous studies [19,20,41]
- Political orientation (0=liberal to 10=conservative), as used in our previous studies [19,20,41]
- Political party (Republican, Democrat, or other), given recent research suggesting divergence between political orientation and party orientation pertaining to face masks [42]
- Race, ethnicity, gender, age ("About how old are you (*in years*)?"), and education level ("What is the highest grade or level of school you have completed, or the highest degree you have received?") [43]

Statistical Analyses

Descriptive statistics of demographics and outcomes will be calculated. We will explore distributions of trust in science (Hypothesis 1) and each of the single-item measures (Hypotheses 2-5).

Data will be analyzed using analysis of covariance (ANCOVA), with the assignment of the study arm (intervention vs control) used as the independent variable and the specified outcomes (depending on the hypothesis) set as the dependent variable. All specified covariates will be included in each model, and assumptions for the analyses will be evaluated (eg, the normality of residuals and linear relationships between covariates and the dependent variable). If assumptions are not met, the research team will explore different transformations or nonparametric models as recommended by statistical experts.

Missingness is not anticipated owing to the study design, but if it occurs at a meaningful level (>5%), we will perform sensitivity analysis using Multiple Imputation by Chained Equations to explore how missingness affects the results, and in the case that the results differ, we will report Multiple Imputation by Chained Equations as the primary analysis.

Data and Code Availability

Raw data will be included as a digital supplement in each format needed to execute the included code (eg, .csv and .sav) alongside the full paper when published. All code needed to replicate the specific data cleaning and analysis steps in this paper will be included as a digital supplement alongside the full paper when published.

Results

This protocol was prepared in full and submitted for review prior to any data collection or subject recruitment. The study will be conducted without using any external funding mechanisms. Results are expected to be published in late 2022 or early 2023.

Discussion

Expected Findings

This study is designed to determine whether the use of normative language in addition to cognitive language has an effect on a variety of measures related to general and specific trust in science and scientists as well as the credibility of the claims and their author(s). As indicated previously, we expect to see lower levels of general and localized trust in science and as well as reduced perceptions of credibility of both the post and the scientist(s) conducting the study among study participants who are exposed to both a cognitive and normative claim about a study than those exposed only to a cognitive claim.

Next Steps

If 1 or more of our hypotheses are correct, then we hope to use these findings to initiate discussions about research dissemination and communication and the ways in which communication about research findings might more closely attend to and explicitly draw distinctions between cognitive and normative claims. This discussion may include conversations around changing the ways in which scientists communicate generally and addressing the complexity of separating normative and cognitive claims when communicating outside of the field (eg, with the media or policy makers).

We plan to disseminate the results of this study regardless of the findings through peer-reviewed publications as well as other avenues, as appropriate.

Limitations

We anticipate that this study design may result in several limitations to its interpretation. First, we cannot control the conditions in which people participate; thus, although we will incorporate comprehension checks for the intervention, we cannot be assured that all participants will sufficiently engage with the intervention content. Second, since this is a web-based study through the Prolific platform, even though the results have a degree of national US generalizability, they still reflect the unique characteristics of those who have signed up for the Prolific platform as well as, by extension, those who actively use the internet. In a recent protocol for our COVID-19 intervention study, we outline why we believe these concerns are somewhat attenuated for this type of experiment [44]. Other limitations may be identified during the study itself or by reviewers at each stage of the project and will be noted after their identification.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed in the preparation of this protocol.

Authors' Contributions

JA contributed to conceptualization, project administration, resources, visualization, and writing the original draft. YX and LGA contributed to formal analysis. JA, YX, and LGA contributed to the methodology. All authors contributed to investigation, validation, and writing—review and editing.

Conflicts of Interest

None declared.

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Protocol

The Impact of the COVID-19 Pandemic on Perinatal Loss Experienced by the Parental Couple: Protocol for a Mixed Methods Study

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Abstract

Background: At the beginning of 2020, mothers and fathers who experienced perinatal events (from conception to pregnancy and postpartum period) found themselves facing problems related to the emergency caused by the COVID-19 pandemic and the associated difficulties for health care centers in providing care. In the unexpected and negative event of perinatal loss (ie, miscarriage, stillbirth, and neonatal death) more complications occurred. Perinatal loss is a painful and traumatic life experience that causes grief and can cause affective disorders in the parental couple—the baby dies and the couple's plans for a family are abruptly interrupted. During the COVID-19 pandemic, limited access to perinatal bereavement care, due to the lockdown measures imposed on medical health care centers and the social distancing rules to prevent contagion, was an additional risk factor for parental mental health, such as facing a prolonged and complicated grief.

Objective: The main aims of this study are as follows: to investigate the impact of COVID-19 on mothers and fathers who experienced perinatal loss during the pandemic, comparing their perceptions; to evaluate their change over time between the first survey administration after bereavement and the second survey after 6 months; to examine the correlations between bereavement and anxiety, depression, couple satisfaction, spirituality, and sociodemographic variables; to investigate which psychosocial factors may negatively affect the mourning process; and to identify the potential predictors of the development of complicated grief.

Methods: This longitudinal observational multicenter study is structured according to a mixed methods design, with a quantitative and qualitative section. It will include a sample of parents (mothers and fathers) who experienced perinatal loss during the COVID-19 pandemic from March 2020. There are two phases—a baseline and a follow-up after 6 months.

Results: This protocol was approved by the Ethics Committee of Psychological Research, University of Padova, and by the Institutional Ethics Board of the Spedali Civili of Brescia, Italy. We expect to collect data from 34 or more couples, as determined by our sample size calculation.

Conclusions: This study will contribute to the understanding of the psychological processes related to perinatal loss and bereavement care during the COVID-19 pandemic. It will provide information useful to prevent the risk of complicated grief and psychopathologies among bereaved parents and to promote perinatal mental health.

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KEYWORDS

COVID-19 pandemic; perinatal loss; bereavement care; mourning; anxiety; depression; posttraumatic stress disorder; COVID-19; pandemic; psychological; bereavement; miscarriage; stillbirth; neonatal death; parent; experience; coping; grief

Introduction

Background and Rationale

The COVID-19 pandemic has seen almost 500 million people infected with the disease, including more than 6 million deaths globally [1]; it has also caused a global health, social, and economic crisis, with negative effects on the general population. Lockdown measures imposed to curb the spread of the infection [2] led to physical and emotional isolation, and this resulted in a global situation of uncertainty and psychological distress [3-5].

The COVID-19 pandemic also had collateral effects on mental health [6,7], with an increase in mental disorders in the general population [8] and mainly affecting the most vulnerable [9]. There are indeed indications that the adverse effects of health and social disasters are greater among vulnerable groups, such as the perinatal population [10]. The perinatal population is particularly vulnerable [11-13]—the period from conception to pregnancy and postpartum, which involves physiological, psychological, and social changes [14-16] and presents complex challenges for women [17] and men [18] who "transition to parenthood" [19]. Screenings over the prenatal and postnatal period [20] demonstrate that parents (mothers and fathers) may experience affective disorders [21] such as anxiety [22,23] and depression [24,25], also with comorbidity [26], with the risk of negative consequences for the mother's health (eg, risks of miscarriage, pre-eclampsia, and gestational hypertension), and negative effects on the child's development (premature birth; lower appearance, pulse, grimace, activity, and respiration scores; and low birth weight) [27] and on parents-infant relationships [28-30].

Due to the COVID-19 pandemic, these risk factors increased in the perinatal period; there were interruptions to the provision of perinatal health care services and changes to their structure [31,32]. During pregnancy, checkups and many routine outpatient visits were canceled [33,34], and there was a reduction in obstetric and psychological follow-ups. Delivery procedures during the pandemic also changed [35], with fathers not allowed to assist during labor. Lockdown and social isolation, together with restricted visits to maternity wards during hospitalization, in an effort to limit the risk of transmission of the virus, which reduced contact with family members, increased the negative psychological impact on the mother due to the lack of perceived social support [36,37]. Social support from the partner was also affected [38,39], as fathers were almost always not allowed to accompany mothers for checkups in health care centers. Preterm newborns were isolated from their mothers and fathers in the neonatal intensive care unit [40]. The pandemic restrictions also affected the immediate postpartum period, with interruptions in early dyadic relationships, particularly in mother-infant attachment [41]. International literature on COVID-19 effects reports mental health implications and distress in women during pregnancy [42], delivery, and postpartum [38,43], with an increasing prevalence of perinatal depression, anxiety [44-46], and posttraumatic stress disorders [47]. Pregnant mothers' anxiety of attending checkups in clinics during routine prenatal care, due to the fear of being infected by SARS-CoV-2, and uncertainty about the effect of the virus on the fetus and infant, led to the postponing or cancelling of routine medical health care appointments [48], even though there was no consistent evidence of potential vertical intrauterine transmission of COVID-19 from mother to fetus [49,50]. The data collected by international researchers are controversial due to the lack of knowledge about the virus, which has generated many uncertainties about its long-term effects.

During the pandemic health emergency, maternal and fetal outcomes worsened globally, although there are limited data indicating that SARS-CoV-2 infection caused higher levels of adverse perinatal outcomes [51,52], measured in infected pregnant women compared to noninfected pregnant women [53]. Adverse outcomes include increased risks of perinatal loss [54,55]. Perinatal loss, that is, miscarriage (>20 weeks), stillbirth (>20 weeks gestation), or neonatal death (newborn in the first 28 days of life) [56], is an unexpected and complex negative life event, an experience that has always been poorly investigated. If we consider the period prior to the COVID-19 pandemic, more than 2 million perinatal deaths (*stillbirths*) and 2.9 million neonatal deaths occur worldwide every year [57]. However, The Lancet reports that not all of these deaths are recorded [58], and in the countries where the highest mortality occurs, the cause of these deaths is often not even identified. It should be noted that this high incidence has an economic impact on both global health and social systems [59]. Only recently did the World Health Organization [60] issue an operational guide to Maternal and Perinatal Death Surveillance and Response.

Perinatal death causes grief for the parental couple, requiring bereavement care [61]. In the international literature, "perinatal loss" refers to the death of the child in the perinatal period, but the term "loss" does not describe the parents' state of mind and the complex psychological aspects of their suffering caused by this death. Perinatal loss is a painful and traumatic experience that can negatively affect a couple's life; when the child dies, the plans for a new arrival in the family are abruptly halted, and the couple must process their mourning [62-65]. This interior processing of the grief over death is a necessary event, and the extent of their suffering depends on the affective investment of the parental couple in the child [66-69].

The possible negative consequences in terms of parental health can include affective disorders, such as anxiety, depressive, psychosomatic, and posttraumatic stress disorders [70]. Bereavement can lead to a crisis of faith [71], and the literature confirms that this can also occur in perinatal loss [72,73]. Perinatal loss is a biologically negative event, a particularly inexplicable experience; in the order of life events, children outlive their parents, hence the suffering of bereaved parents.

Spirituality can serve as a coping mechanism to soften the complex painful feelings by helping mourners adapt to loss, and spiritual practices have been associated with better adjustment after the death of a child [71]. In a recent Italian study involving women who have experienced perinatal loss, it was found that religion helps them to accept grief and give meaning to such a tragedy [61].

There is a strong emotional impact also on the health care professionals working in maternity units [72,74]. It is important that these professionals understand parental perceptions to prevent the onset of psychopathologies, as perinatal mortality is an experience in which the early activation of the grief process is exacerbated by the circumstances surrounding this event [75].

During the pandemic period, mothers and fathers who suffered a perinatal loss found themselves experiencing further problems relating to COVID-19 [76], with the associated difficulties of the health system. Inpatient care for perinatal loss consists of bereavement care [77] according to specific clinical guidelines [78,79], which health care professionals were unable to follow during the pandemic to support parents. COVID-19 restrictions affected the provision of bereavement care compared to the period before the pandemic [80]. Personal protective equipment also prevented expressions of empathy from the operators, and support by means of physical contact was no longer permitted. There was also no time to train health workers adequately so that they could deal with the changes appropriately. These changes in care caused resentment among parents [81] and raised concerns over the possible negative impact on the long-term mourning process for parents and families [82] and increased risk of complicated grief [83].

The University of Padova and the University of Brescia propose a multicenter study, based in Italy, to optimize scientific knowledge in the field of studies of the effects of the COVID-19 pandemic on the perinatal period. There is a paucity of studies evaluating the psychological impact of the COVID-19 pandemic on couples experiencing the loss of their child in the perinatal period.

Objectives

The main aims of this study are as follows:

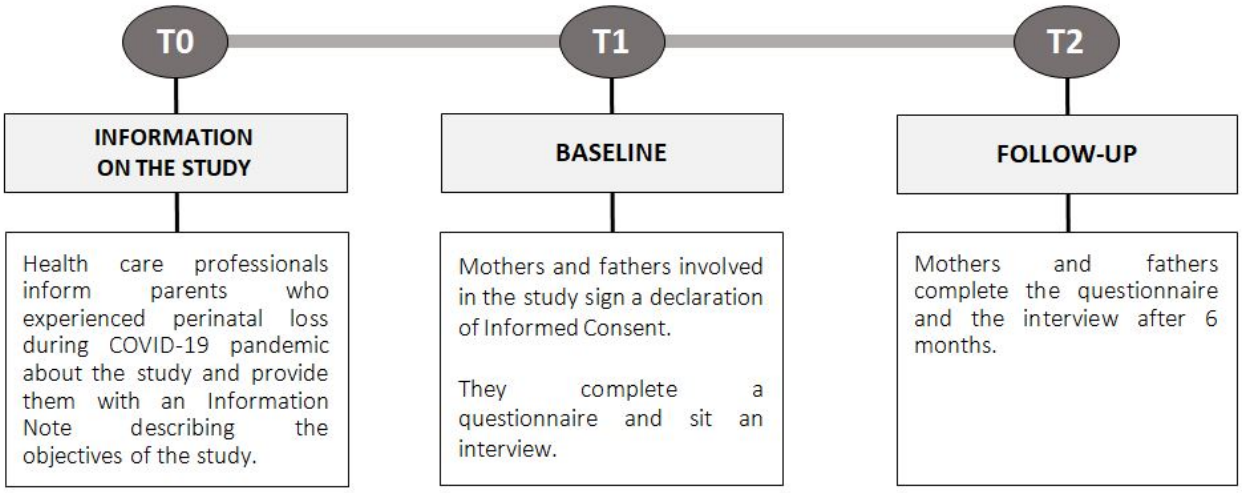
- To investigate the impact of COVID-19 on mothers and fathers who experienced perinatal loss during the COVID-19 pandemic, comparing mothers' and fathers' perceptions
- To evaluate the change over time for fathers and mothers between the first survey after bereavement and the second survey, after 6 months
- To examine correlations of bereavement with anxiety, depression, couple satisfaction, spirituality, and sociodemographic variables. The main hypothesis is that the trauma was severe, to a greater extent for mothers, with outcomes of anxiety and depression. It is also hypothesized that more negative outcomes are related to difficult relationships, and this combination of traumatic experiences can lead to a crisis of faith, thus reducing the chances of resorting to religion as a coping mechanism
- To investigate which psychosocial factors negatively affect the mourning process, and identify the potential predictors of the development of complicated grief

Methods

Study Design

This longitudinal observational multicenter study is structured according to a mixed methods design, with a quantitative and qualitative part. The timeline of the whole procedure is shown in Figure 1. The study comprises two phases, which are a baseline (Figure 1: T1) and a 6-month follow-up (Figure 1: T2).

Figure 1. Timeline.



Recruitment

Health care professionals (psychologists, psychotherapists, psychiatrists, midwives, etc) will conduct the study at health care centers throughout Italy (counseling centers, hospitals, etc) and the facilities involved and coordinated by the Observatory of Perinatal Clinical Psychology of the University of Brescia (Table 1). Among the mothers and fathers attending the health care centers, health care professionals will identify those who have experienced perinatal loss since the beginning of the

COVID-19 pandemic (from March 2020) and will inform them about the study (Figure 1: T0). Health care professionals will provide mothers and fathers with an information note describing the aims of the study and will ask them to sign a declaration of informed consent if they intend to participate in the study. The first data collection time point (Figure 1: T1) will be after the death of the child, as soon as the parental couples are available to participate in the study, considering the difficulties due to the trauma for their perinatal loss. To protect their privacy, parents who agree to participate will be assigned a code with which they will become part of the study (participants can authorize the communication of their name to the research centers). Health care professionals will communicate the code or name of individuals participating to the Observatory of Perinatal Clinical Psychology of the University of Brescia. Both health care professionals and recruited participants will take part in this study voluntarily and without compensation.

Table 1. Health care professionals and health care centers, as well as facilities involved and coordinated by the Observatory of Perinatal Clinical Psychology of the University of Brescia.

Location	Unit type and name	Health care professionals
Bergamo	• ASST[a] Bergamo Est; Obstetrics OU[b]	• 1 PsyD[c]
Brescia	• ASST Spedali Civili Hospital; Clinic and Family Centers	• 1 PsyD • 2 Psychologists • 2 Midwives
Como	• Specialist Clinic of Perinatal Psychology	• 2 PsyDs
Enna	• Umberto I Hospital; Obstetrics and Gynecology OUC[d]	• 1 PsyD
Florence	• LHA[e] of Toscana Centro; Family Clinic	• 2 PsyDs
Lodi	• ASST Lodi; Obstetrics OU	• 1 Midwife
Mantua	• ASST Mantua Carlo Poma Hospital; Maternal and Child Department • Clinical Psychology; Obstetrics and Gynecology OUC and NICU[f]	• 2 PsyDs
Lecco	• Arcobaleno and Pep Nursery School	• 1 Educationalist
Padua	• Kairos Donna Association	• 1 Psychologist
Palermo	• Buccheri La Ferla Hospital and Georgia Association	• 1 PsyD
Turin	• LHA 3 of Turin; Specialist Centers of Perinatal Psychology	• 1 PsyD
Venice	• Specialist Clinic of Perinatal Psychology	• 1 PsyD
Vicenza	• ULSS8 Berica; Mental Health Department	• 1 Psychiatrist

[a]ASST: Azienda Socio Sanitaria Territoriale.

[b]OU: unit or department.

[c]PsyD: psychologist-psychotherapist.

[d]OUC: operating unit complex.

[e]LHA: local health authority.

[f]NICU: neonatal intensive care unit.

Eligibility Criteria

Mothers and fathers who experienced perinatal loss during the COVID-19 pandemic form March 2020 and who are proficient in Italian are included in the study.

The main exclusion criterion is mental health—participants must not be diagnosed with a mental disorder by a psychiatrist and must not be undergoing psychiatric or psychopharmacological treatment.

Materials and Procedure

In this Study, the participants (mothers and fathers) will be invited to participate in two phases of data collection. In the first phase (Figure 1: baseline—T1) they will perform the following:

- Complete a questionnaire (quantitative instrument) by the University of Brescia, which will be administered by the health professionals. The responses to the questionnaire will be entered by the health professionals directly into a web-based survey. Researchers at the University of Brescia

will verify the quality of the data and coordinate the network of health professionals.
- Sit an interview (qualitative instrument) administered by specialized and trained researchers from the University of Padova, for consistency. The interview will be analyzed using thematic analysis [84].

In the second phase of data collection (Figure 1: follow-up—T2, after 6 months), mothers and fathers will be asked to complete the questionnaire and the interview by health care professionals. All data collected at each step will be deidentified and stored in a secure, password-protected drive with access only available to the research team members.

Study Outcomes

The primary outcome for this study is the impact of the COVID-19 pandemic on the grief of mothers and fathers who experienced a perinatal loss during the pandemic. The secondary outcomes are the changes in social and couple relationships, maternal or paternal affectivity and satisfaction, spirituality, trauma, grieving strategies, and unhelpful or helpful factors. The tertiary outcomes relate to understanding the type of responsibility that parents ascribe to COVID-19 with respect to their perinatal loss.

Quantitative Measurement (Survey)

Sociodemographic Assessment Form for Mother or Father

The Sociodemographic Assessment Form has been designed to collect the mother's or father's sociodemographic data (ie, age, nationality, academic qualifications, professional status, economic situation, and current marital status) and anamnestic data (ie, date of birth; week of gestational age of the baby at the time of delivery; health facility where the birth took place; number of pregnancies; possible abortions; any mental disorders diagnosed; psychological therapies in progress; medication taken for depression, anxiety, or other problems; and perceived social support, eg, from family, friends, health services).

COVID-19—the Impact of Event Scale-Revised

The Impact of Event Scale-Revised [85] is a 22-item self-report tool that assesses subjective distress caused by traumatic events. Respondents are asked to identify a specific stressful life event and then indicate the degree of distress they felt over the following 7 days by each "difficulty" listed. Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The Impact of Event Scale-Revised yields a total score (ranging from 0 to 88), and subscale scores can be calculated for the Intrusion, Avoidance, and Hyperarousal subscales.

Prolonged Grief-13

The Prolonged Grief-13 [86] is a self-administered questionnaire consisting of 13 items, which evaluates the diagnosis of prolonged bereavement. The result is calculated based on an algorithm consisting of the following five criteria: (1) event of the loss; (2) separation distress (items 1-2); (3) duration (item 3); (4) cognitive, emotional, and behavioral symptoms (items 4-12); and (5) significant functional impairment, 6 months after loss (item 13). All five criteria must be met to diagnose prolonged grief disorder. The total score on the prolonged grief symptom scale is obtained by summing criteria (2) and (4).

Perinatal Assessment of Paternal or Maternal Affectivity

The Perinatal Assessment of Paternal or Maternal Affectivity [21] is a 10-item self-report questionnaire that investigates the following 8 dimensions: anxiety, depression, perceived stress, irritability or anger, relationship problems (eg, in couple, family, with friends, and at work), behavioral alterations of illness (eg, somatization, functional medical syndromes, and hypochondriac complaints), physiological disorders (eg, sleep, appetite, or sexual desire disorders), addictive disorders, and behavioral acting out. Some questions related to the paternity or maternity experience and the possible influence of sociocultural factors are included. The responses are indicated with an X on an analog line, with a rating from "Not at all" to "Very." The line has small points, each of which corresponds to a score from 0 to 10. The tool allows us to identify fathers or mothers who have a significant risk of manifesting perinatal affective disorders. It is very simple to administer and quick to fill in, is suitable for different contexts, and is usable by professionals with different skills, both in public and private care settings.

Dyadic Adjustment Scale Brief Version

The Dyadic Adjustment Scale brief version [87] is a shortened version of the Dyadic Adjustment Scale. It is a self-report tool for evaluating couple satisfaction and is composed of the following 4 items: three items are on a 6-point Likert scale, ranging from 0 (all the time) to 5 (never), while the final item is on a 7-point scale ranging from 0 (extremely unhappy) to 6 (perfect).

Daily Spiritual Experiences Scale

The Daily Spiritual Experiences Scale [88] is a self-report tool composed of 16 items with 6-point Likert response (1=never; 6=many times), and it examines the dimension of the perception of the transcendent in the individual and their perception of interaction with the transcendent in daily life.

Inventory of Complicated Spiritual Grief

The Inventory of Complicated Spiritual Grief [89] measures how much individuals specifically consider the level of loss experienced when responding to indicators of spiritual crisis that affect their relationship both with God and with fellow worshipers. It is composed of 18 items (Annex 5) with a 5-point Likert response scale (0=not true at all and 4=absolutely true). The factorial analysis highlighted a 2-factor structure, as follows: (1) "Insecurity with God," which is composed of 7 items that investigate the individual's insecurity toward their relationship with God, and (2) "Disruption in Religious Practice," which is composed of 11 items that investigate how far the individual has abandoned religious practices.

Qualitative Measurement (Interview)

Thematic Analysis

Thematic analysis [84] has been widely used in mixed methods design, because it can be applied to a broad range of epistemologies and research questions, enabling researchers who use different research methods to communicate with each other [90]. It is a method for identifying, analyzing, organizing, describing, and reporting themes identified within a qualitative data set [84], producing trustworthy and insightful findings [91].

Sample Size Estimation

The primary endpoint of this study is the impact of the COVID-19 pandemic on the grief of mothers and fathers who experienced a perinatal loss during the pandemic. Considering a power (1-β) of 0.80 and a type I error (α) of .05, a sample of 34 parental couples is needed. The sample size is extremely low, but it will be in line with literature studies on perinatal loss that include and analyze small samples of couples [92,93]. As indicated by literature [94], the mixed methods design can help studies that involve small samples.

Analysis

Quantitative and qualitative analysis will be carried out for the questionnaires and interviews. Appropriate data analysis will be performed using standard statistical packages.

Quantitative Data Analysis

The following steps will be performed: (1) descriptive analysis of all questionnaires prepared for the mother and father and evaluation of the differences between mother and father using 2-tailed *t* test for matched pairs. The results of the power analysis conducted using the GPower program indicate that comparison of the averages for fathers and mothers assuming an average effect, an alpha level of .05, and a power of .80 requires at least 34 couples; (2) evaluation of the change over time for mother and father between the first survey (after bereavement) and second survey (after 6 months) using repeated measured ANOVA. The results of the power analysis conducted using the GPower program indicate that comparison of the averages over time (2 measurements over time), for fathers and mothers assuming an average effect, an alpha level of .05, and a power of .80 requires at least 34 couples; (3) preliminary examination of the bivariate correlations between the measurements examined in the study and the sociodemographic variables using Pearson correlation; and (4) define a multiple regression model with the main predictive variables of the management of perinatal bereavement (including only the variables found to be significant in the preliminary examination). The results of the power analysis conducted using the GPower program indicate that a multiple regression model capable of explaining a significant share of the variability of the scores of the dependent variable, assuming a medium-sized effect, an alpha level of .05, and a power of .80, requires at least 92 people, including 5 predictors in the model, and at least 118 people, including 10 predictors in the model. Finally, if we manage to reach the number of 100 participants, estimating between 10% and 15% attrition, we will be able to proceed as described.

Qualitative Data Analysis

Participants (ie, the father and mother) will be asked to sit a semistructured interview that will further explore the issues investigated by the questionnaires. Parent interviews will be carried out separately via the Zoom platform. The interviews will be fully recorded and transcribed verbatim to be analyzed with the support of the Atlas.ti software. A thematic analysis will be carried out on the transcripts to identify the main common themes among the interviewees. We will focus on recognizable convergences and specificities through an appropriate comparison of the texts. The emerging themes identified within the experiences narrated by the participants will allow researchers to create a shared codebook within which the sentences stated by the participants will be assigned to a category according to the identified theme. The analysis will follow the 6 basic phases of preparation, generation of categories or themes, data encoding, verification of emerging understanding, search for alternative explanations, and drafting of the report. To verify the accuracy of the analysis and the interpretative procedures adopted by the interviewer and the supervisor, 2 other members of the research team will work on the texts until an agreement is reached between all researchers. The Atlas.ti software will be used to facilitate the identification of themes and will facilitate the creation of network graphics to describe the logical relationships between the concepts and categories identified by the researchers.

Ethics Approval

Our study protocol was reviewed and approved by the Ethics Committee of Psychological Research, University of Padova (N. 3989 - 09/02/2021), and by the Institutional Ethics Board of the Spedali Civili of Brescia, Italy (N. NP4858 - 07/10/2021). All procedures performed in this study are in accordance with the ethical standards of the Institutional Ethics Board of the Spedali Civili of Brescia, and with the Declaration of Helsinki 1964 and subsequent amendments. We shall obtain written consent from the parents.

Patient and Public Involvement

The parents were not involved in the design, conduct, reporting, or dissemination plans of this research.

Confidentiality Procedure and Access to Data

Personal information about potential and enrolled participants will be collected only by members of the research team and cannot be accessed by other individuals. Personal information and survey data will be pseudonymized using an identification number. Only authorized study personnel will have access to any of the data associated with this study.

Results

According to our sample size calculation, we expect that at least 34 couples from health care centers located in Italy will participate in the study.

We will publish all results in peer-reviewed international journals indexed in Web of Science or Scopus databases and present them at national and international conferences.

Discussion

Overview

The COVID-19 pandemic forced health services to redefine perinatal bereavement care protocols [78,79] due to the restrictions imposed to curb the spread of the virus. However, health care professionals were unprepared for these changes [31,32], which led to an increase in perinatal affective disorders in mothers and fathers [70], who felt isolated and lacking social support [36,37] at such a challenging time. To our knowledge,

the impact of COVID-19 on care following the death of a baby has not been sufficiently explored.

This multicenter study will contribute to optimize the scientific knowledge in the field of studies of the impact of the COVID-19 pandemic on pregnancy and particularly on mothers and fathers grieving for a perinatal loss. It will contribute to the understanding of the psychological processes related to perinatal loss, bereavement care, and mourning during the COVID-19 pandemic; it will also provide information useful to preventing the risk of prolonged and complicated grief and parent psychopathologies and will promote perinatal mental health.

Regarding the implications in clinical practice, it would seem important to implement psychological services in health care centers (eg, counseling centers and obstetrics and gynecology wards) that can offer adequate support to mothers, fathers, and families who are experiencing the unexpected and painful event of perinatal loss of their child, especially if this happens in difficult and complex situations such as a global health emergency.

This study could pave the way for future scientific research in the same or similar area of interest that should consider perinatal bereavement, an event still poorly investigated and not always socially recognized, to develop a strong support system for the affected mothers, fathers, and families.

Limitations

The most likely limitation of this study could be that some parents contacted by health care professionals may not agree to participate because the perinatal loss event may have been too traumatic and painful, and they may not want to talk about it anymore after it happened. Concerning data collection time point, recruited parental couples may not have experienced perinatal loss in the same week of pregnancy or in the same neonatal period, and this could be another limitation of this study. What the sample couples share is that the perinatal loss event occurred during the COVID-19 pandemic. Lastly, the sample, composed only of parents who speak and understand the Italian language, may be too small to be able to generalize the results.

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Data Availability

Data sharing does not apply to this article as data sets will not be generated or analyzed in this article.

Authors' Contributions

IT and LC contributed equally to the general study design. LC and AT coordinate and manage the implementation of the study at each health care center. AT verifies the quality of the quantitative data. EI administers the interviews and processes the qualitative data. IT conceptualized the study, the statistical plan, and qualitative analysis. LR conducts the statistical analysis. LC and AT drafted the first version of the manuscript. IT revised the draft of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Protocol

Feasibility, Acceptability, and Protective Efficacy of Seasonal Malaria Chemoprevention Implementation in Nampula Province, Mozambique: Protocol for a Hybrid Effectiveness-Implementation Study

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Abstract

Background: Seasonal malaria chemoprevention (SMC) is a highly effective community-based intervention to prevent malaria infections in areas where the malaria burden is high and transmission occurs mainly during the rainy season. In Africa, so far, SMC has been implemented in the Sahel region. Mozambique contributes 4% of the global malaria cases, and malaria is responsible for one-quarter of all deaths in the country. Based on recommendations in the Malaria Strategic Plan, the Malaria Consortium, in partnership with the National Malaria Control Programme in Mozambique, initiated a phased SMC implementation study in the northern province of Nampula. The first phase of this 2-year implementation study was conducted in 2020-2021 and focused on the feasibility and acceptability of SMC. The second phase will focus on demonstrating impact. This paper describes phase 2 of the implementation study.

Objective: Specific objectives include the following: (1) to determine the effectiveness of SMC in terms of its reduction in incidence of malaria infection among children aged 3 to 59 months; (2) to determine the chemoprevention efficacy of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) when used for SMC in Nampula Province, Mozambique, and the extent to which efficacy is impacted by drug resistance and drug concentrations; (3) to investigate the presence and change in SP+AQ–and piperaquine-resistance markers over time as a result of SMC implementation; and (4) to understand the impact of the SMC implementation model, determining the process and acceptability outcomes for the intervention.

Methods: This type 2, hybrid, effectiveness-implementation study uses a convergent mixed methods approach. SMC will be implemented in four monthly cycles between December 2021 and March 2022 in four districts of Nampula Province. Phase 2 will include four components: (1) a cluster randomized controlled trial to establish confirmed malaria cases, (2) a prospective

cohort to determine the chemoprevention efficacy of the antimalarials used for SMC and whether drug concentrations or resistance influence the duration of protection, (3) a resistance marker study in children aged 3 to 59 months to describe changes in resistance marker prevalence over time, and (4) a process evaluation to determine feasibility and acceptability of SMC.

Results: Data collection began in mid-January 2022, and data analysis is expected to be completed by October 2022.

Conclusions: This is the first effectiveness trial of SMC implemented in Mozambique. The findings from this trial will be crucial to policy change and program expansion to other suitable geographies outside of the Sahel. The chemoprevention efficacy cohort study is a unique opportunity to better understand SMC drug efficacy in this new SMC environment.

Trial Registration: ClinicalTrials.gov NCT05186363; https://clinicaltrials.gov/ct2/show/NCT05186363

International Registered Report Identifier (IRRID): DERR1-10.2196/36403

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KEYWORDS

malaria; chemoprevention; children; protocol; Nampula; Mozambique; feasibility; effectiveness; mixed methods; SMC; SP+AQ; hybrid effectiveness; cRCT

Introduction

Overview

The World Health Organization (WHO) defines seasonal malaria chemoprevention (SMC) as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness, with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk [1-5]. It involves administering monthly courses of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) during this peak transmission period to those most at risk: children 3 to 59 months of age [6]. SMC has been demonstrated to be a highly effective intervention that can prevent up to 75% of malaria cases in eligible children [7]. It has also been shown that the intervention can be delivered safely at scale, achieving high coverage [8,9]. To date, SMC has only been adopted and scaled up in Sahelian countries of West and Central Africa, following the WHO recommendation for this region to be the first to implement SMC. However, in many parts of East and Southern Africa, there remain concerns over widespread resistance to SP, which may reduce the effectiveness of SMC [10,11]. However, it has been suggested that SP may retain its protective efficacy even in areas where resistance is high [12,13].

Mozambique accounts for 4% of global malaria cases, and the disease is highly endemic in the entire country, with the highest prevalence in the north and along the coast [14-16]. According to surveys conducted in Mozambique, the national prevalence of malaria in children aged 6 to 59 months remained stable at 38% in 2011 [17], 40% in 2015 [18], and 39% in 2018 [19]. The prevalence varies across the country, with it being higher in the northern and central provinces and lower in the southern provinces. Nampula was one of the provinces with the highest prevalence of malaria (65%-66%) in 2015. However, a slight decrease was observed in 2018 to 48%, but it remained one of the highest prevalence rates after Cabo-Delgado (57%) [19]. Among chemoprevention strategies implemented in Mozambique, for more than 10 years, the Mozambique Ministry of Health and the National Malaria Control Programme (NMCP) have been actively implementing intermittent preventive treatment in pregnancy using SP [18].

To date, in Mozambique, studies about delivery of intermittent preventive treatment in infants (IPTi) with SP have been conducted and have been paired with the Expanded Programme on Immunization during routine contacts [20,21]. Even though different research studies about the resistance of SP in sub-Saharan Africa exist in the literature, there is no robust evidence about the impact of resistance on the efficacy of intermittent prevention treatments as an SMC strategy in the region [2,22] or IPTi in Mozambique [23]. A midterm review of the country's Malaria Strategic Plan 2017-2022 recommended SMC as a strategy to accelerate the impact of treatment in the highest-burden locations [24]. To assess whether SMC can be an effective malaria prevention strategy in an area where resistance to SP is assumed to be high, the Malaria Consortium, in partnership with the NMCP in Mozambique, initiated a phased SMC implementation project in Nampula Province. The project was designed as a 2-year hybrid effectiveness-implementation study that took place over two consecutive phases.

Phase 1

The first phase focused on exploring the feasibility and acceptability of SMC outside of the Sahel [25]. It was conducted between November 2020 and February 2021 and involved administering four monthly cycles of SMC to a target population of around 72,000 children in two districts of Nampula Province, Malema, and Mecubúri. SMC delivery followed the standard door-to-door delivery model commonly used in Sahelian countries, with trained volunteers acting as community distributors, supervised by health facility workers. A third district, Lalaua, where SMC was not implemented served as a control area. Research activities included the following:

1. Documentation of how the SMC implementation model used in the Sahel was adopted to the local context.
2. A representative end-of-round household survey to assess coverage and quality of delivery,
3. Interviews and focus group discussions with key stakeholders.

4. A quality assessment of health management information system (HMIS) data on malaria indicators reported at the health facility and district levels.
5. A nonrandomized controlled trial to estimate the ratio of the hazard of developing one or more episodes of malaria during SMC cycles among a sample of children in an intervention district compared to the hazard in the control district.
6. A study of molecular resistance markers to determine baseline prevalence of SP and AQ resistance and any increase in resistance prevalence after one annual round of SMC [25].

While data analysis is ongoing, preliminary results suggest that SMC is a feasible and acceptable intervention and that it confers protection from malaria to eligible children. Detailed results from phase 1 will be published elsewhere.

Phase 2

The second phase will focus on demonstrating impact by addressing feasibility and effectiveness of SMC and chemoprevention efficacy. This protocol describes phase 2 of the implementation study.

Objectives

Phase 2 aims to test the feasibility, effectiveness, and chemoprevention efficacy of SMC with SP plus AQ (SP+AQ) in Nampula Province in Mozambique, where malaria transmission is highly seasonal. Specific objectives include the following:

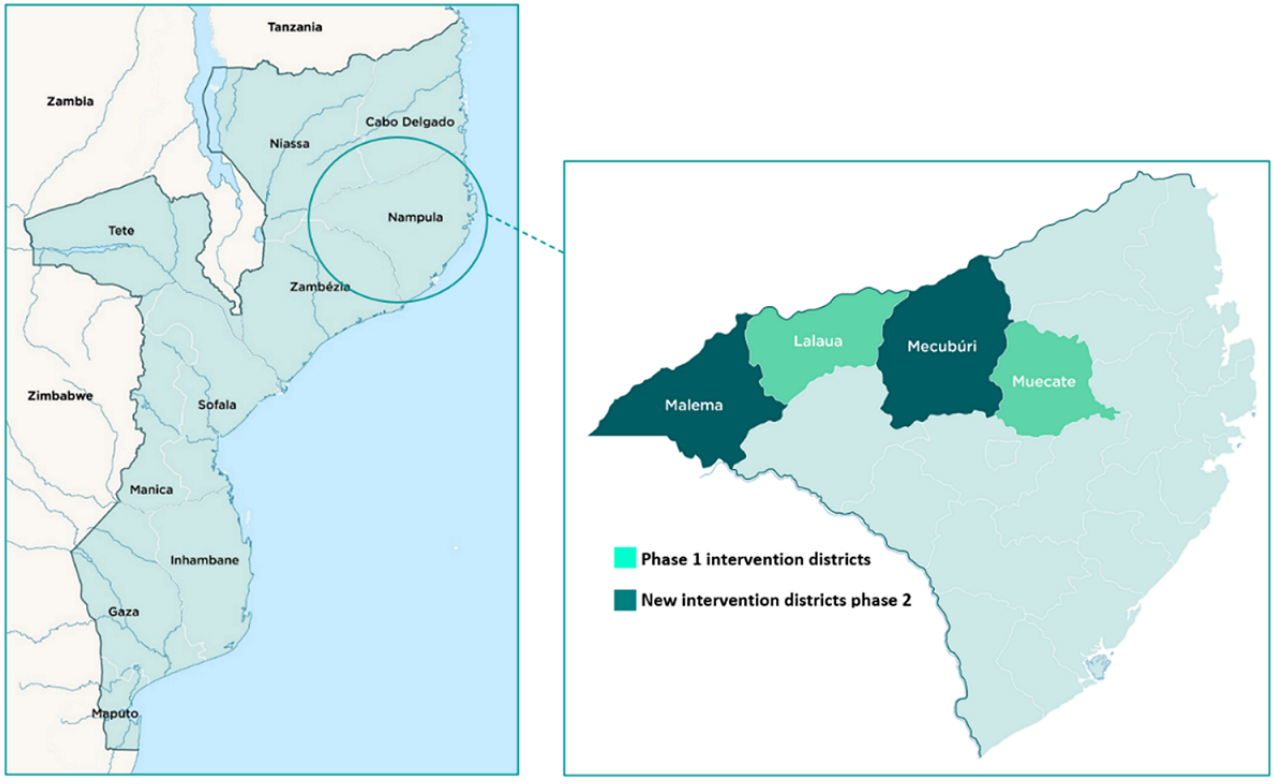
1. To determine the effectiveness of SMC in reducing the incidence of malaria infection among children aged 3 to 59 months.
2. To determine and measure efficacy as follows:
   a. To determine chemoprevention efficacy of SP+AQ when used for SMC in Nampula Province, Mozambique.
   b. To calculate the extent to which efficacy is impacted by drug resistance and drug concentrations.
3. To investigate the presence and change of SP+AQ– and piperaquine-resistance markers over time as a result of SMC implementation.
4. To understand the impact of the SMC implementation model by determining process, costing, and acceptability outcomes for the intervention.

Methods

Study Design

This type 2, hybrid, effectiveness-implementation study uses a convergent mixed methods approach [26]. As the study includes components of clinical effectiveness and implementation research, a type 2, hybrid, effectiveness-implementation design was selected. These designs provide benefits over pursuing these lines of research independently; for example, they offer more rapid translational gains, more effective implementation strategies, and more useful information for decision makers. SMC will be implemented in four monthly cycles between January 2022 and April 2022 in four districts of Nampula Province (Figure 1): Malema and Mecubúri, where phase 1 of the study was conducted, will continue to receive SMC in phase 2; Lalaua, the control area in phase 1, and Muecate will receive SMC for the first time in phase 2. The research will involve the following components:

Figure 1. Intervention districts in Nampula Province, Mozambique.



1. Conducting a cluster randomized controlled trial (cRCT) through passive surveillance to establish confirmed malaria cases among participating children.
2. Conducting a prospective chemoprevention efficacy cohort study to determine whether SP+AQ provides 28 days of protection from infection, and whether drug concentrations and resistance influence the duration of protection.
3. Conducting a resistance marker study in children aged 3 to 59 months in the two research districts plus the two standard intervention districts to describe changes in resistance marker prevalence over time.
4. Conducting a process evaluation of the SMC implementation looking at cost and process outcomes.

Study Setting

Individual elements of the study will be conducted in all four districts. The cRCT and process evaluation will be conducted in Lalaua and Muecate districts in Nampula Province, Northeastern Mozambique (Figure 1). The chemoprevention efficacy cohort study will be conducted in communities within the catchment area of one health facility in Lalaua district. The resistance marker study will be conducted in all four districts. As part of the process evaluation, several key informant interviews may be conducted with stakeholders who are based in Maputo.

To identify suitable districts for SMC implementation, a suitability ranking was conducted in-country with oversight from the WHO for all provinces. Criteria included a variety of factors: (1) seasonality eligible for SMC (ie, 60% of rainfall concentrated into 4 months), (2) mortality (ie, areas of highest mortality in children younger than 5 years using HMIS data), (3) access to care (ie, highest ranking given to areas where access to care was lowest), and (4) treatment-seeking behavior (ie, highest ranking given to areas where treatment-seeking behavior was lowest). The average category score was used to determine a final ranking and identify the top 20 suitable districts for maximizing the impact of SMC. From the list of suitable districts, additional consideration was given based on the importance of implementing the intervention in an area where no other new interventions were taking place so that effects could be attributable to only the intervention under investigation. Districts in Nampula Province were selected, as no indoor residual spraying or new long-lasting insecticide-treated net distribution campaigns had been targeted to these areas, allowing for a more robust attribution of SMC impact on malaria.

Study Population

The study population that is eligible to receive SMC includes afebrile children [1] of either gender (ie, children with a fever on the day of SMC administration will be excluded and referred to the health facility for further evaluation), aged 3 to 59 months for any of the SMC cycles, and residing in any of the four districts. Children must be 59 months or younger at the start of the first cycle; if they turn 5 years old during the SMC season, they may continue to receive SMC. If children are 2 months old or younger at the first cycle month, they can begin SMC once they are 3 months old in any cycle. During phase 1, when only Mecubúri and Malema districts were included, population data were retrieved from the National Census 2017, adjusting by an annual growth factor of 3.5% in Nampula Province, as calculated by the National Institute of Statistics. For phase 2, population figures for Mecubúri and Malema were obtained through the administrative coverage data of SMC from phase 1. For the two new districts, Lalaua and Muecate, as it was done for districts in phase 1, population figures were retrieved from the 2017 census data, projected for 2021 and considering a growth rate of 3.5% per year (Table 1). Additionally, health workers involved in SMC implementation; caregivers of children younger than 10 years of age; community leaders and key stakeholders, such as health officials at different levels of the health system; and those involved in SMC implementation will be sampled to provide information with regard to the intervention, according to the different study elements.

Table 1. Estimated target population of seasonal malaria chemoprevention (SMC) districts.

District	Population[a] for each eligible children's group by age, n		
	3-11 months	12-59 months	All children
Malema	8500	35,800	44,300
Mecubúri	7300	36,000	43,300
Lalaua	3200	13,600	16,800
Muecate	1900	8000	9900
All districts	20,900	93,400	114,300

[a]District populations were determined by the National Institute of Statistics and SMC 2021 coverage data.

Ethical Considerations

Ethical approval for this study was received from the Comité Nacional de Bioética para a Saùde (CNBS) of the Mozambique Ministry of Health on December 22, 2021 (reference No. 803/CNBS/21), and by the Research Ethics Committee of the Hospital Clinic of Barcelona on December 20, 2021 (reference No. HCB/2021/0944). Only participants who meet the inclusion criteria and whose caregivers provide written informed consent will be included in the study. The trial has been registered at ClinicalTrials.gov (NCT05186363).

Primary and Secondary Outcomes

The primary outcomes for the different elements are presented below by component.

Cluster Randomized Controlled Trial

The primary outcome for this component of the protocol is the incidence of confirmed malaria cases using a rapid diagnostic test (RDT) reported through passive surveillance. Secondary outcomes include severe anemia, as an indication of severe malaria, and parasitemia levels, both gametocyte carriage rates and density of *Plasmodium falciparum* trophozoites and *P Falciparum* gametocytes.

Chemoprevention Efficacy Study

The primary outcome is chemoprevention failure in the presence of adequate drug concentration and associated parasite genotype, as defined by quantitative polymerase chain reaction (qPCR)–positive parasites on day 28 or a positive malaria slide at any time from day 7. Secondary outcomes include uncomplicated malaria within the first 28 days, hospitalization within the first 28 days, and severe malaria within the first 28 days.

Resistance Marker Study

The primary outcome is the prevalence of relevant SP+AQ– and piperaquine-associated antimalarial resistance phenotypes: *P falciparum* dihydrofolate reductase gene (*Pfdhfr*)—codons 51, 59, 108, and 164; *Pfalciparum* dihydropteorate synthetase gene (*Pfdhps*)—codons 431, 437, 540, 581, and 613; *Pfalciparum* chloroquine resistance transporter gene (*Pfcrt*)—codons 72 to 76; and *Pfalciparum* multidrug resistance gene 1 (*Pfmdr1*)—codons 86, 184, and 1246.

Sample Sizes

Cluster Randomized Controlled Trial

Clusters will be selected for the intervention arm at the community level in two districts. The study will be powered to have an 80% chance of detecting a significant reduction in RDT-confirmed malaria incidence at the 5% confidence level using a chi-square test comparing two independent proportions in a cluster randomized design. We are aiming to detect a significant reduction in malaria incidence from 0.2 to 0.12 clinical episodes per child per high-transmission season, corresponding to the SMC round. The clinical episodes should be of sufficient severity to present to a health facility, and the reduction in episodes should be equivalent to an odds ratio of 0.66, or a minimum effect size of 33%. This is based on the assumption that the efficacy of SP+AQ in Northern Mozambique, where the prevalence of resistance alleles in circulating parasites is high, is half of that found in studies in West African settings. To account for the cluster randomized design, we assumed an intracluster correlation for malaria outcomes within communities of 0.23, based on data from SMC coverage surveys conducted by the Malaria Consortium in 2020 [27] and 2021 [28]. A cluster size of 15 children per community was selected, and children in the intervention and control arms were recruited in a ratio of 1:1.5. This resulted in a total sample size of 2850 eligible children in 190 clusters: 1710 in 114 clusters in the control arm and 1140 in 76 clusters in the intervention arm. A total of 76 communities from a list of all communities will be selected as intervention districts using a simple random method. Then, 114 communities will be selected at random from among those remaining for inclusion in the control arm.

Chemoprevention Efficacy Cohort Study

We aim to recruit participants from within Lalaua district, one of the new phase 2 implementation districts. Assuming a 3% breakthrough infection rate, sampling 494 children will provide a 95% CI of 1.7% to 4.9%. Assuming a 99% response rate and 1% loss to follow-up, a sample size of 500 children is considered appropriate. We assume that the drug resistance observed for all drugs (ie, SP+AQ) will be the same across a 300-km radius from the location. Therefore, selecting a single health facility should introduce no selection bias when we consider drug resistance prevalence across the region.

Resistance Marker Study

The sample size for the survey was determined using a sample size calculation from a WHO protocol for drug efficacy testing [29], with the intention to estimate changes in prevalence of SP- and AQ-resistance markers with enough precision to provide adequate power to detect changes if they occur. A sample of 300 children per district—150 each at baseline and end line—is expected to result in 90% power to detect a difference at the 5% confidence level in sextuple SP mutants from less than 1% to 2%. In Lalaua, where the chemoprevention efficacy study will be conducted, we determined that a sample of 600 children—300 each at baseline and end line—is needed to obtain a sufficiently accurate specific prevalence measure in the absence of data on malaria parasite ecologies. This will result in a total sample size across both districts of 1500, with 750 children sampled at both baseline and end line.

Recruitment and Data Collection

Cluster Randomized Controlled Trial

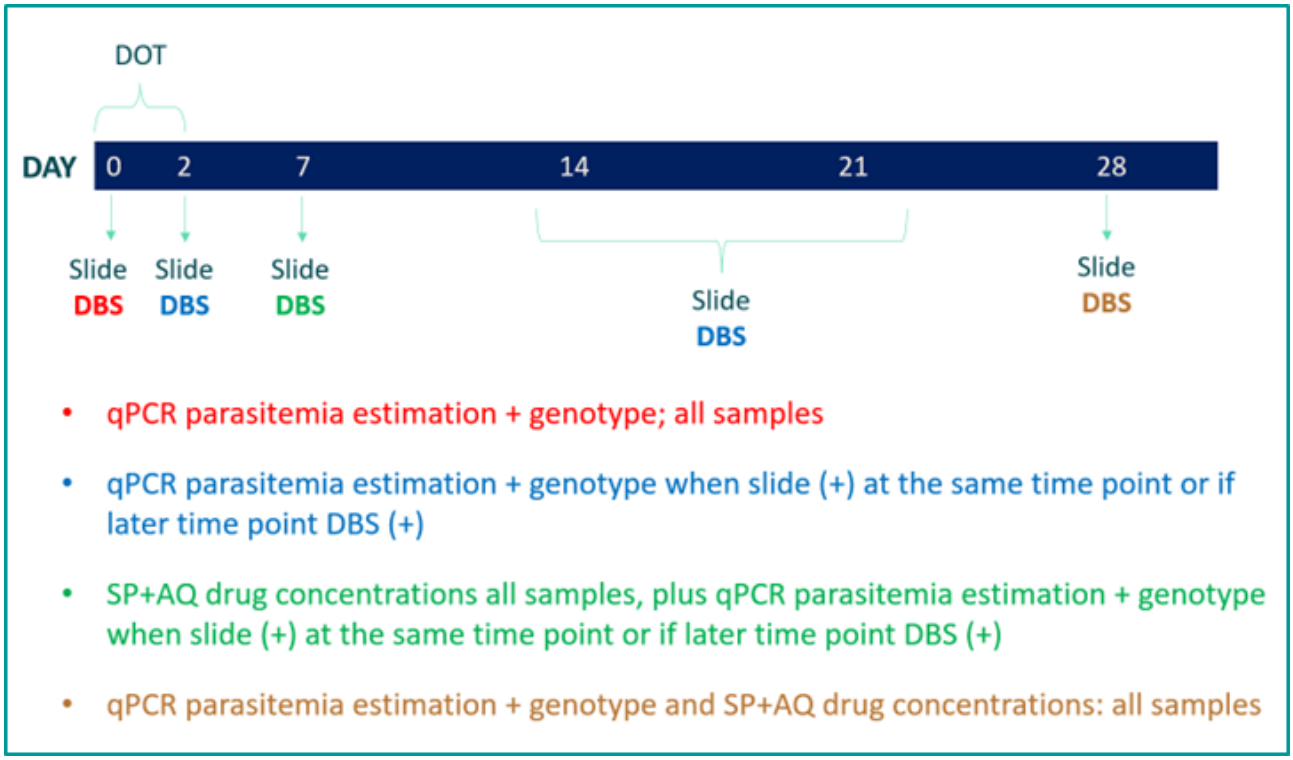
In the control arm in both districts, compounds will be randomly sampled by researchers using household lists from selected communities, with one eligible child recruited at random from each household. After caregivers provide consent, children will be recruited and a short baseline questionnaire will be administered to collect individual data on each child and to confirm their eligibility. In the intervention arm, a researcher will follow a pair of community distributors as they administer SMC. In addition to variables such as experiences of fever within the past month among selected children, data on a range of variables relating to the selected child, their caregiver, and their household will be collected as part of the survey. These variables will include the selected children's age, sex, and use of mosquito nets as well as the caregivers' and heads-of-household's level of education, occupational position, literacy level, household size, wealth (using the Simple Poverty Scorecard), primary language, and migration status, among other variables. Data on these variables will be collected in order to include potential confounders in the analysis for the association between the receipt of SP+AQ and clinically significant malaria. Children will be given SP+AQ by community distributors via directly observed therapy; in addition, blood samples will be taken and subsequent hemoglobin concentration measured using a HemoCue system (HemoCue AB). Children recruited into the study presenting at

clinics will be identified using unique identification numbers and barcodes, and data on clinic visits, including suspected malaria cases and results of RDTs, will be matched to baseline questionnaire data to build a database for analysis.

Chemoprevention Efficacy Cohort Study

This component will investigate the chemoprevention efficacy of SP+AQ at current dosing regimens among SMC-eligible children. Following the WHO's Malaria Chemoprevention Efficacy Study Protocol [30], both malaria thick smears and dried blood spots (DBSs) will be taken at day 0, day 2, day 7, day 14, day 21, and day 28 during and after administration of the first cycle of SP+AQ, which will be administered through directly observed therapy. All DBS samples on day 0 and day 28 will be processed to ascertain low-density parasitemia estimates through qPCR. If sufficient DNA exists, day-0 and day-28 samples will be genotyped and compared. If children are found to have the same haplotype, this will indicate a recrudescent infection. If different haplotypes are present or if there is presence of an infection on day 28 that was not present on day 0, this will indicate a new infection after SP+AQ administration. Day-7 samples will also be processed for drug levels of all three SMC drugs, and day-28 samples will be processed for SP and AQ. The qPCR methodology is primed to detect presymptomatic parasitemia of clinical relevance. More sensitive PCR methodologies will not be conducted in order to prevent detection of extremely low–level parasitemia that will not be of clinical significance. DBSs will also be processed for estimates of blood parasite density and genotyping of relevant drug-resistance markers on days 2, 7, 14, and 21 if a child's thick smear on those days was positive or if DBSs at a later time point are *P falciparum* positive. A DBS will also be collected whenever a child has a fever and is positive on a malaria RDT based on histidine-rich protein 2 and plasmodium lactate dehydrogenase. Drug level, qPCR parasite estimation, and genotyping will also take place. A blood smear will not be taken, as the RDT diagnosis will be sufficient when associated with fever. An RDT will not be given to children on day 0 unless they have signs and symptoms of malaria as per the standard SMC protocol, in which case they will be excluded from the study sample (see Figure 2 for an illustration of the proposed sample collection time points and subsequent sample processing sequence). We aim to recruit participants from within Lalaua, one of the new phase 2 research districts.

Figure 2. Proposed sample collection time points and subsequent sample processing sequence. DBS: dried blood spot; DOT: directly observed therapy; qPCR: quantitative polymerase chain reaction; SP+AQ: sulfadoxine-pyrimethamine plus amodiaquine.



Resistance Marker Study

Trends in SP and AQ resistance will be monitored in the two original intervention districts, as well as in the two research districts. Additionally, in the new phase 2 areas, the prevalence of *Pfalciparum* plasmepsin 2 (*Pfplm2*) will be determined to inform future studies on appropriate use of dihydroartemisinin piperaquine for chemoprevention. A health facility–based, cross-sectional survey will be conducted before SMC project implementation (ie, baseline) and after one complete round of SMC distribution (ie, end line). Monitoring the prevalence of alleles associated with resistance to drugs is, by standard protocol, performed by collecting samples from symptomatic children with evidence of infection. The sample collection will be performed in four selected health facilities in each study district. The key markers to be monitored are as follows: *Pfdhfr*—codons 51, 59, 108, and 164; *Pfdhps*—codons 431, 437, 540, 581, and 613; *Pfcrt*—codons 72 to 76; *pfmdr1*—codons 86, 184, and 1246; and *Pfplm2*.

Data Analysis

Cluster Randomized Controlled Trial

First, the characteristics of the eligible children in the intervention and control arms will be described and tabulated; these analyses will use survey weights obtained using population estimates for each community cluster. Next, a chi-square test will be performed to determine whether there is a significant difference in the proportions of children in each arm experiencing at least one confirmed malaria case during the study period, and exact odds ratios will be calculated.

Random-effects Cox proportional hazards regression models will then be fitted to estimate the difference in risk of an RDT-confirmed malaria case over time of follow-up; results will be expressed as hazard ratios, and a percentage effect size will be calculated. Model diagnostics will be run to verify the proportional hazards assumption, and random effects will be modeled at the community level to account for within-cluster correlation in malaria outcomes.

Two types of models will be fitted. The first will model risk of malaria based on time to first malaria case during each child's first continuous period of follow-up; those experiencing an RDT-confirmed malaria case will be considered dropped from the sample, whereas those lost to follow-up will be considered right-censored. The second model type will account for recurrent events—using random effects for follow-up periods nested within individual children's data—with children experiencing a malaria case considered to be "recovered" on the day of case confirmation and will continue to contribute follow-up information after this event.

Finally, to adjust for potential confounders, covariates based on data obtained from the baseline recruitment survey will be added sequentially to each of these two models by forward stepwise selection.

Chemoprevention Efficacy Cohort Study

Distributions and proportions of relevant mutations will be analyzed to compare the chemoprevention efficacy between groups of mutations. The blood drug concentrations will be analyzed as a cohort by mean, median, and SD, and statistical tests of their associations with treatment outcome—in particular, drug concentrations on day 7—will be performed. The focus will be on outliers with low levels of drug concentration based on the outcome measures described. Day-28 positivity will be associated with antimalarial drug resistance genotype.

Resistance Marker Study

Prevalence of *Pfdhps*, *Pfdhfr,Pfcrt*, and *Pfmdr1* alleles in parasites obtained from participating children will be ascertained. Copy numbers of *Pfplm2* will also be quantified.

Availability of Data and Materials

The associated study protocol and data collection tools will be made available upon request from the corresponding author. Quantitative data sets are available from the corresponding author upon reasonable request after the completion of primary analyses and results dissemination. Qualitative study data sets will not be available, as they may include identifiable information that could comprise participant confidentiality.

Results

Data collection began in mid-January 2022 and concluded in mid-June 2022. Data analysis is expected to be completed by October 2022.

Discussion

Principal Findings

This hybrid research protocol will provide information about the feasibility, effectiveness, and chemoprevention efficacy of SMC using SP+AQ in Nampula, a northern province of Mozambique, where malaria transmission is high and seasonal.

The results from phase 1 of the Mozambique SMC implementation study demonstrated that SMC with SP+AQ is safe, feasible, and acceptable in the local context. The intervention was successfully delivered according to schedule and at the anticipated scale, achieving high coverage [28]. No serious adverse events were reported. Acceptability of the intervention among the population was high, with no negative rumors reported. The intervention appears to be highly effective: in a nonrandomized controlled trial, children who lived in a district where SMC had been implemented had 86% lower odds of developing clinical malaria during the peak transmission season compared with children who lived in the control district without SMC implementation [31]. There were high rates of sulfadoxine and pyrimethamine resistance, but one annual round of SMC does not appear to have had a negative impact on the resistance profile.

In phase 2 of the study, more work is needed to understand the efficacy of SP+AQ to clear existing infections and prevent new infections. This is what we mean by the term "chemoprevention efficacy." The phase 2 chemoprevention cohort will determine whether SP and AQ in combination using current dosing regimens for SMC-eligible children are able to prevent infections over a 28- to 31-day period between cycles during the high-transmission season. Importantly, this cohort will also determine whether these drugs can also clear asymptomatic malaria to provide an estimate of chemoprevention efficacy in terms of prevention of both new and recrudescent infections. This will help determine the duration of effectiveness of SP+AQ. Further work is also crucially needed to map antimalarial drug resistance in these key populations in Mozambique, which has already been frequently highlighted in the literature [32]. The relationship between chemoprevention effectiveness and chemoprevention efficacy and how it relates to drug resistance is currently unclear. The chemoprevention efficacy component of this study aims to elucidate that relationship within the context of Northern Mozambique. The intention is to create a system where the relationship between these variables is better understood within and across malaria ecologies. We may find that drug resistance across Northern Mozambique and how it relates to effectiveness and efficacy covers a large geographical area, but this must be confirmed through future work once we better understand the dynamics of these interactions. Therefore,

in the process of validating this methodology and analyzing these dynamics, it is prudent to create a geographical restriction to the assumptions of this protocol, whereby resistance to SP, in particular, may be representative of a given parasite population [13].

The study will also provide robust evidence of the effectiveness of SMC in an area outside of the Sahel in the form of a randomized controlled trial. This is the first time this work will have been done outside the Sahel and will prove crucial to national and global policy change. This study will support the extension of SMC outside Sahel geographies as already outlined by the WHO [33]. Work in close collaboration with key stakeholders, including the NMCP, the Mozambique Ministry of Health, and the Mozambique National Institute of Health, will ensure that clear and consistent recommendations will be provided in order to produce robust guidance for the national malaria control strategy. Findings will be presented at the province and district levels during meetings led by the research team and local stakeholders; these will involve community leaders, community distributors, and health professionals. Key messages will be provided to the audience, who will have the opportunity to give feedback regarding the development of new actions to secure continuity. Findings will also be presented during the next Mozambique Regional Scientific Days edition in 2023. Finally, results will be disseminated in peer-reviewed scientific journals and on the official Malaria Consortium website.

Limitations

Administration of SP+AQ to ineligible children older than 59 months may raise concerns in relation to the development of drug resistance, as doses administered are unlikely to offer sufficient protection against malaria transmission. This also influences the secondary data analysis in the same way; administering SP+AQ to children older than 59 months could reduce the apparent effect size in the targeted age group.

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Conflicts of Interest

None declared.

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Abbreviations

AQ: amodiaquine
CNBS: Comité Nacional de Bioética para a Saùde
cRCT: cluster randomized controlled trial
DBS: dried blood spot
HMIS: health management information system
IPTi: intermittent preventive treatment in infants
NMCP: National Malaria Control Programme
***Pfcrt*:** *Plasmodium falciparum* chloroquine resistance transporter gene
***Pfdhfr*:** *Plasmodium falciparum* dihydrofolate reductase
***Pfdhps*:** *Plasmodium falciparum* dihydropteorate synthetase
***Pfmdr1*:** *Plasmodium falciparum* multidrug resistance gene 1
***Pfplm2*:** *Plasmodium falciparum* plasmepsin 2
qPCR: quantitative polymerase chain reaction
RDT: rapid diagnostic test
SMC: seasonal malaria chemoprevention
SP: sulfadoxine-pyrimethamine
SP+AQ: sulfadoxine-pyrimethamine plus amodiaquine
WHO: World Health Organization

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Protocol

Mindfulness-Based Stress Reduction, Cognitive Behavioral Therapy, and Acupuncture in Chronic Low Back Pain: Protocol for Two Linked Randomized Controlled Trials

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Abstract

Background: Nonpharmacologic mind-body therapies have demonstrated efficacy in low back pain. However, the mechanisms underlying these therapies remain to be fully elucidated.

Objective: In response to these knowledge gaps, the Stanford Center for Low Back Pain—a collaborative, National Institutes of Health P01–funded, multidisciplinary research center—was established to investigate the common and distinct biobehavioral mechanisms of three mind-body therapies for chronic low back pain: cognitive behavioral therapy (CBT) that is used to treat pain, mindfulness-based stress reduction (MBSR), and electroacupuncture. Here, we describe the design and implementation of the center structure and the associated randomized controlled trials for characterizing the mechanisms of chronic low back pain treatments.

Methods: The multidisciplinary center is running two randomized controlled trials that share common resources for recruitment, enrollment, study execution, and data acquisition. We expect to recruit over 300 chronic low back pain participants across two projects and across different treatment arms within each project. The first project will examine pain-CBT compared with MBSR and a wait-list control group. The second project will examine real versus sham electroacupuncture. We will use behavioral, psychophysical, physical measure, and neuroimaging techniques to characterize the central pain modulatory and emotion regulatory systems in chronic low back pain at baseline and longitudinally. We will characterize how these interventions impact these systems, characterize the longitudinal treatment effects, and identify predictors of treatment efficacy.

Results: Participant recruitment began on March 17, 2015, and will end in March 2023. Recruitment was halted in March 2020 due to COVID-19 and resumed in December 2021.

Conclusions: This center uses a comprehensive approach to study chronic low back pain. Findings are expected to significantly advance our understanding in (1) the baseline and longitudinal mechanisms of chronic low back pain, (2) the common and distinctive mechanisms of three mind-body therapies, and (3) predictors of treatment response, thereby informing future delivery of nonpharmacologic chronic low back pain treatments.

Trial Registration: ClinicalTrials.gov NCT02503475; https://clinicaltrials.gov/ct2/show/NCT02503475

International Registered Report Identifier (IRRID): PRR1-10.2196/37823

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KEYWORDS

mind-body therapies; chronic low back pain; nonpharmacologic treatments; neuroimaging

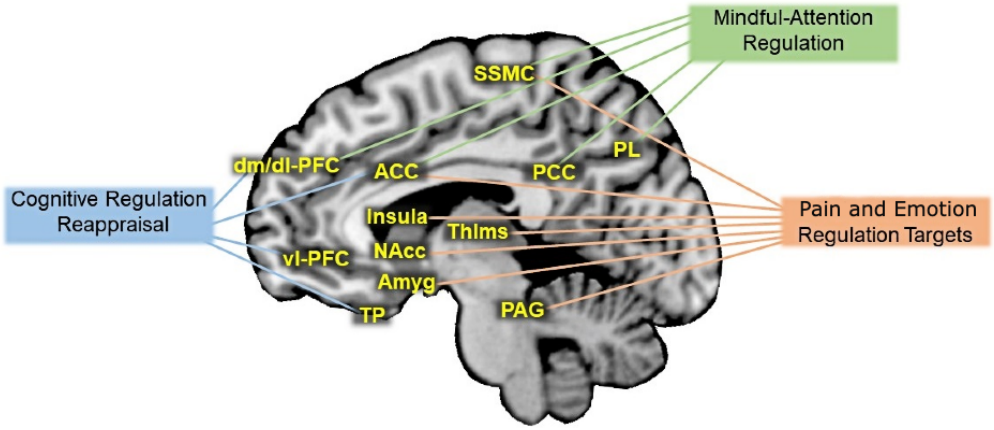
Introduction

An astounding 50 million to 100 million Americans live with ongoing pain, with approximately 20 million enduring high-impact chronic pain that includes substantially restricted work, social, and self-care activities [1-3]. Chronic low back pain is cited as the most common type of chronic pain condition [3].

Globally, chronic low back pain has an estimated prevalence of 10% to 20% in adults [4,5], is the leading cause of disability [6,7], and is one of the most clinically and economically burdensome medical conditions [3,8-10]. Despite the availability and increased use of traditional surgical, pharmacological, and physical treatments [11,12], the prevalence of chronic low back pain continues to increase at an alarming rate [6,13], and the health of individuals with chronic low back pain is deteriorating [3,14].

Researchers have increasingly appreciated that chronic low back pain involves central nervous system abnormalities that cause, maintain, and amplify pain [15-20]. Acupuncture and other prominent "mind-body" treatments, such as cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR), effectively engage participants in daily symptom self-management that impacts the central nervous system; these treatments offer low-risk, evidence-based, and economical therapies for this disabling condition [21-30]. However, there is a need to better characterize the underlying common and distinctive neurophysiological mechanisms of different mind-body treatments. Researchers can apply knowledge of these mechanisms to better optimize therapies targeted at an individual's unique characteristics. Furthermore, this mechanistic information can serve as predictive biomarkers for whether a patient will be responsive to a particular mind-body therapy. A promising class of potential mechanisms relate to emotional reactivity and emotion regulation systems. Indeed, there is growing appreciation that these systems play a significant role in the perception, chronicity, and treatment efficacy of pain [17,31-35]. Research has established a clear link between emotion regulatory systems and pain perception in the brain (Figure 1) [36-46]. Importantly, CBT, MBSR, and acupuncture engage these same brain systems [28,29,47-52].

Figure 1. Schematic depiction of brain regions commonly involved in cognitive regulation reappraisal, mindful-attention regulation, and targets for pain and emotion regulation. ACC: anterior cingulate cortex; Amyg: amygdala; dm/dl-PFC: dorso medial and dorso lateral prefrontal cortex; NAcc: nucleus accumbens; PAG: periaqueductal gray; PCC: posterior cingulate cortex; PL: parietal lobe; SSMC: somatosensory motor cortex; Thlms: thalamus; TP: temporal pole; vl-PFC: ventro lateral prefrontal cortex.



Pain-CBT is tailored to meet the specific needs of a person living with chronic pain. It includes pain education, relaxation training, cognitive restructuring, and behavioral interventions to target and modify maladaptive pain beliefs, reduce emotional reactivity, and increase adaptive emotion regulation strategies to enhance descending modulation of pain. Randomized controlled trials (RCTs) demonstrate the acceptability and short- and long-term efficacy of pain-CBT [30,53-61], and pain-CBT is a recommended first-line treatment for chronic low back pain [62].

MBSR targets early attentional processes to enhance an experiential approach toward the ongoing stream of thoughts, emotions, and sensations, through formal and informal meditation practices [63-65]. MBSR RCTs have demonstrated short- and long-term clinical benefits by improving physical function and health-related quality of life, and by reducing pain intensity, pain unpleasantness, and disability [30,53,54,66-72].

Based on traditional Chinese medicine, acupuncture consists of inserting fine metallic needles through the skin and into specific locations along pathways considered to be special conduits for electrical signals, to stimulate and restore the body's "vital energy" [73-75]. A meta-analysis [76] and systematic reviews [30,77] concluded that acupuncture is effective for pain reduction. Electroacupuncture uses small electric currents,

passed between pairs of needles, to stimulate acupuncture points in a standardized fashion. Preclinical and animal studies suggest that electroacupuncture might be more effective at relieving chronic pain than manual acupuncture [78].

Although research and RCTs indicate a positive effect of these mind-body treatments, their common and distinct mechanisms, their relative treatment efficacy, and the suitability of specific treatment components to specific subgroups remain unclear [79]. In response to these knowledge gaps, the National Center for Complementary and Integrative Health (NCCIH) funded the Stanford Center for Low Back Pain (grant P01AT006651), which was established as one of two Centers of Excellence for Research on Complementary and Alternative Medicine (CERCs). The second CERC was awarded to the Massachusetts General Hospital (grant P01AT006663) [80-83]. Here, we provide an overview of the design and implementation of the Stanford Center for Low Back Pain and the two RCTs aimed at characterizing the mechanisms of chronic low back pain treatments.

Methods

Scientific Focus

The Stanford Center for Low Back Pain will conduct two linked RCTs to elucidate the underlying mechanisms of pain-CBT, MBSR, and electroacupuncture for chronic low back pain, with a specific focus on the intersection of pain modulatory and emotion regulatory systems.

Researchers have identified that emotions are subject to diverse regulatory processes [84-86], such as cognitive regulation and attention regulation (Figure 1). Cognitive regulation uses language-based reasoning strategies to reconstrue the meaning of an emotion-eliciting situation to up- or down-modulate features of emotion instantiated in the ventral emotion system. Attention regulation modifies alerting, orienting, and executive attention [87]. Attention regulation involves training to focus on a selected object while inhibiting irrelevant distracter stimuli. Cognitive regulation is thought to be an active mechanism in pain-CBT, whereas attention regulation is thought to be an active mechanism in MBSR. These regulatory processes form the basis for investigating the effects of mind-body therapies in these linked RCTs.

The first RCT extends and expands on previous RCTs by replicating the efficacy of pain-CBT and MBSR for chronic low back pain treatment [53,54,88] and assessing the behavioral and neural mechanisms underlying their impact on pain. We will elucidate how these therapies differentially enhance the behavioral and neural indices of cognitive regulation and attention regulation during evoked pain, prospectively, and in comparison with wait-list (WL) participants with chronic low back pain that undergo no treatment.

The second RCT will evaluate the mechanisms underlying electroacupuncture treatment of chronic low back pain. We will compare how verum (ie, real) and sham electroacupuncture for chronic low back pain impact temporal summation and conditioned pain modulation, as measures of ascending pain facilitation and descending pain inhibition, respectively (see Kong et al [89] for specific trial protocol). As with the first RCT, we will characterize the impact of electroacupuncture on emotion regulatory processes using cognitive regulation and attention regulation during evoked pain. We expect the scientific knowledge gained by this CERC to translate to improved pain intervention for chronic low back pain.

Stanford Center for Low Back Pain Organization

We organized the Stanford Center for Low Back Pain to promote cross-project collaborations, maintain recruitment consistency, enhance synergies across projects, provide common assessments and analyses, and optimize resource sharing. To facilitate administration, study execution, data collection, and analyses, the multidisciplinary projects will be supported by an Administrative Core, Clinical Research Core, Behavioral Core, and Neuroimaging and Psychophysics Core. The Administrative Core provides logistical and scientific coordination among the Scientific Cores and related individual projects. The Clinical Research Core supports scientific collaboration by focusing on regulatory submissions and oversight, participant recruitment and preliminary screening, participant safety, centralized data management and biostatistics, and education about human research. The Clinical Research Core will be the first contact for recruitment and preliminary screening of interested participants. This core will internally monitor recruitment progress, support data quality assurance, and perform between-project analyses to develop overall predictive models. The Behavioral Core will administer all behavioral measures (eg, validated questionnaires on pain, function, mood, expectancy, and quality of life) and oversee the pain-CBT and MBSR therapies. The Neuroimaging and Psychophysics Core will support all projects with a common battery to capture critical outcome measures administered by trained personnel using specialized psychophysics equipment. The battery consists of psychophysics (eg, evoked pain, temporal summation, and diffuse noxious inhibitory control) components. The neuroimaging aspect of the core will support acquisition, storage, and analysis of the structural and functional neuroimaging data.

Study Design

Overview

The study includes two thematically related, prospective, single-center RCTs. Trial 1 compares pain-CBT versus MBSR versus no treatment; trial 2 compares verum (ie, real) versus sham electroacupuncture. While the RCTs will assess and compare treatment efficacies, the primary goals are to elucidate the underlying mechanisms of the therapies.

Specific Aims

Overview

The aims and hypotheses from the original proposal are described below. We anticipate that this mechanistic study will generate many additional aims and hypotheses using the comprehensive baseline and treatment data.

Aim 1: Assess Immediate and Longer-Term Impact of Pain-CBT Versus MBSR

We will compare pain-CBT–related and MBSR-related improvements in pain symptom severity and well-being in participants with chronic low back pain to each other and to WL-MBSR or WL-CBT participants (1) immediately posttreatment and to each other and (2) at 6 months posttreatment.

Hypothesis 1 is as follows: immediately posttreatment, we expect that both pain-CBT and MBSR will yield greater improvements in pain symptom severity and well-being in chronic low back pain participants compared to WL-MBSR and WL-CBT participants. We expect equivalent improvement for MBSR and pain-CBT immediately and at 6 months posttreatment.

Aim 2: Examine Pain-CBT Versus MBSR Treatment-Related Changes in Cognitive Regulation and Attentional Regulation

We will investigate whether pain-CBT and MBSR differentially enhance behavioral and neural indices of the ability to implement cognitive regulation and attention regulation during evoked low back pain in participants with chronic low back pain.

Hypothesis 2 is as follows: we expect treatment-specific improvements for pain-CBT and MBSR from pre- to posttreatment, as follows: (1) pain-CBT will improve cognitive regulation but not attention regulation and (2) MBSR will improve attention regulation but not cognitive regulation.

Aim 3: Examine Whether Changes in Cognitive Regulation and Attention Regulation Mediate Effects of Pain-CBT and MBSR

We will test whether cognitive regulation and attention regulation changes during treatment and posttreatment mediate pain symptoms and well-being at 6 months posttreatment.

Hypothesis 3 is as follows: we expect that improvement in cognitive regulation will mediate pain-CBT but not MBSR outcomes, and that improvement in attention regulation will mediate MBSR but not pain-CBT outcomes.

Aim 4: Characterize Primary Pain Regulation as a Mediator of Reduction in Back Pain Bothersomeness in Response to Treatment (Primary Clinical Outcome)

Hypothesis 4 is as follows: (1) real versus sham electroacupuncture will lead to greater reduction in temporal summation from baseline to the end of week 4 (ie, after 8 biweekly treatment sessions) and (2) change in temporal summation from baseline to week 4 will mediate reduction in back pain bothersomeness over the treatment course (ie, baseline to posttreatment, around week 10).

Aim 5: Assess Expectation of Benefits (Primary Psychological Measure) as a Moderator of Reduction in Back Pain Bothersomeness in Response to Treatment (Primary Clinical Outcome)

Hypothesis 5 is as follows: participants' expectations of benefits will predict reduction in back pain bothersomeness scores during the treatment period.

Additionally, in the Discussion section, we present several secondary aims and deliverables resulting from this rich data set.

Study Sample and Setting

Across both studies, we aim to enroll more than 300 adults with chronic axial low back pain without radicular symptoms. This sample size accounts for an expected 30% attrition and provides sufficient statistical power for each project. An additional 30 healthy adults will be enrolled for a single neuroimaging visit as the healthy control group. Study screening, enrollment, pre- and posttreatment assessments and procedures, and the pain-CBT and MBSR treatment sessions will take place at the Stanford Systems Neuroscience and Pain Lab of the Stanford Division of Pain Medicine in Palo Alto, California. Verum or sham electroacupuncture sessions will take place in one of 10 acupuncture offices located across the San Francisco Bay Area, based on proximity to each participant. Magnetic resonance imaging (MRI) will occur at the Stanford Lucas Center for Imaging.

Inclusion and Exclusion Criteria

Recruitment will include 21- to 65-year-old men and women with chronic low back pain as determined by the National Institutes of Health (NIH) Task Force on Research Standards for chronic low back pain [90]. Tables 1 and 2 list inclusion and exclusion criteria, respectively, and describe how the criteria will be ascertained. A healthy control group will be recruited consisting of adults with no chronic pain and no medical or mental health condition that would interfere with study procedures. The control group will be age matched (ie, ±2 years) and gender matched to the chronic low back pain group at baseline.

Table 1. Inclusion criteria.

Inclusion criteria	Rationale	Sources
Axial low back pain as primary pain complaint without radicular symptoms	Study restricted to low back pain	A[a], TS[b], S[c]
Pain duration ≥3 months and pain experienced on at least half the days in the past 6 months	As per recent NIH[d] Task Force on Research Standards for Chronic Low Back Pain [90]	A, TS, S
Average pain intensity ≥3/10 for the past 2 weeks after consent	No significant change in level of back pain	A, TS, S
Average pain intensity ≥4/10 for the past month at screening visit	Significant level of back pain to treat and to detect improvement	A, TS, S
English fluency	N/A[e]	A, TS, S
Males and females, 21 to 65 years of age	N/A[e]	A, TS, S

[a]A: automated data gathered from REDCap (Research Electronic Data Capture) surveys.

[b]TS: telephone screening.

[c]S: screening visit.

[d]NIH: National Institutes of Health.

[e]N/A: not applicable; this criterion was also applied to the healthy control group.

Table 2. Exclusion criteria.

Exclusion criteria	Rationale	Sources
Previous CBT[a] or MBSR[b] treatment or similar coursework in the last 2 years, or previous acupuncture treatment for any reason in the past 5 years, respectively, for the two projects[c]	Possible bias due to prior exposure to treatment	A[d], TS[e], S[f]
For the CBT and MBSR project, regular meditation practice (≥2 times/week, ≥15 minutes per meditation session, for ≥6 months) over the last 2 years[c]	Possible bias due to prior exposure to some essential aspects of MBSR	A, TS, S
Participating in any interventional research study or completed participation in the last 2 months; enrollment in an observational study is acceptable[c]	Treatment interference	A, TS, S
MRI[g] contraindications (eg, metal implants and claustrophobia)[c]	MRI safety	A, TS, S
Neurologic disorder, history of seizures, stroke, or brain abnormalities, at the discretion of the study team[c]	Brain integrity interference	A, TS, S
Any radicular symptoms or other comorbid pain syndrome	Study restricted to low back pain	A, TS, S
Any medical condition (eg, active infection and heart disease) that would interfere with study procedures, at the discretion of the study team[c]	Medical conditions may confound mechanistic inferences	A, TS, S
Mental health conditions or treatment for mental health problems that would interfere with study procedures, at the discretion of the study team[c]	Mental health conditions may confound mechanistic inferences	A, TS, S
Medications: starting new medical treatment or medication for pain 2 months prior to initiation of study procedures; opioids ≥60 mg morphine equivalent units/day, anticonvulsants, benzodiazepines, beta-blockers, some antipsychotics, diabetic medications, or other medications that may interfere with study procedures at the discretion of the study team. TCAs[h], gabapentinoids, SSRIs[i], and SNRIs[j] are *not* exclusionary if on a stable dose of at least 2 months[c]	Medications may confound mechanistic inferences	A, TS, S
Ongoing legal or disability claim or worker's compensation (permanent and stationary disability not exclusionary)[c]	Ongoing legal or disability claims may confound mechanistic inferences	A, TS, S
Currently pregnant or planning to become pregnant[c]	Pregnancy may confound mechanistic inferences	A, TS, S
Disorders indicated by the MINI[k] self-report questionnaire will be characterized and participants may be excluded at the discretion of the researcher	Condition that would make it difficult for a person to partake in treatments (eg, suicidality or psychotic disorders)	S

[a]CBT: cognitive behavioral therapy.

[b]MBSR: mindfulness-based stress reduction.

[c]This criterion was also applied to the healthy control group.

[d]A: automated data gathered from REDCap (Research Electronic Data Capture) surveys.

[e]TS: telephone screening.

[f]S: screening visit.

[g]MRI: magnetic resonance imaging.

[h]TCA: tricyclic antidepressant.

[i]SSRI: selective serotonin reuptake inhibitor.

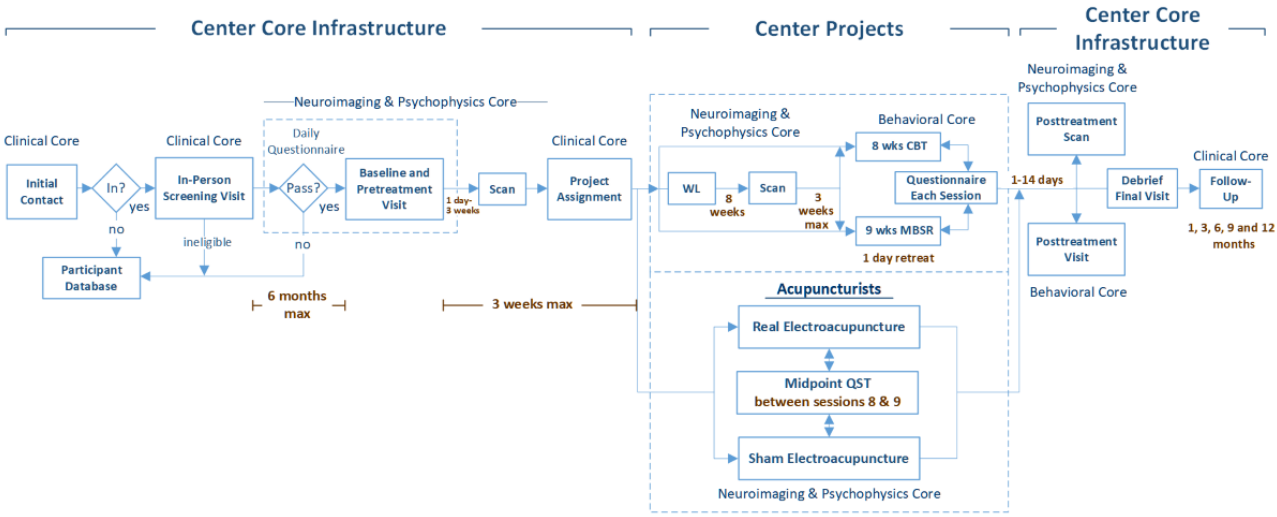
[j]SNRI: serotonin and norepinephrine reuptake inhibitor.

[k]MINI: Mini–International Neuropsychiatric Interview.

Study Procedures

Following initial contact, consent, the in-person screening visit, and eligibility assessment, participants enter one of the two projects (ie, pain-CBT vs MBSR or verum vs sham acupuncture) based on eligibility and preference. Subsequently, after baseline and pretreatment behavioral and neuroimaging assessment (see Figure 2 for participant process), participants will be randomized within each project to a treatment arm (see details below in Randomization section). Immediately posttreatment, participants in both projects will undergo additional behavioral and neuroimaging assessments. Participants will subsequently receive questionnaire assessments 1, 3, 6, 9, and 12 months posttreatment.

Figure 2. Flowchart overview of participant process in the Stanford Center for Low Back Pain project. btw: between; CBT: cognitive behavioral therapy; MBSR: mindfulness-based stress reduction; mo.: month; QST: quantitative sensory testing; wks: weeks; WL: wait-list.



Ethics Approval

The study protocols were approved for human subject research by the Stanford Institutional Review Board (reference Nos. 22436 and 11689).

Recruitment and Screening

Participants will be recruited from social media marketing, the Stanford Systems Neuroscience and Pain Lab database, and local advertisements in clinics and in the community. All advertisements will direct interested individuals to complete a secure, online REDCap (Research Electronic Data Capture [91]) self-screening form for initial eligibility screening. Responding individuals will be contacted by phone for additional screening and, if potentially eligible, will be invited to an on-site consent and screening visit for further eligibility assessment. During this visit, the Mini–International Neuropsychiatric Interview (version 7.0) [92] will be administered, and additional study-specific criteria will be assessed (Tables 1 and 2). We will subsequently use experiential sampling methods, requiring each potential participant to provide daily feedback on pain symptoms, emotional functioning, and general health and well-being for a 3-week period after consent. Participants who do not adequately provide daily feedback will be excluded prior to randomization.

Randomization

Eligible participants will be assigned to a project based on current recruitment needs and randomized within each project separately. For example, to maximize participant retention in the pain-CBT and MBSR groups we prioritize recruitment for that cohort several weeks before the start of the treatment course. If a participant is unwilling to participate in a particular project (ie, pain-CBT or MBSR or electroacupuncture), they will be assigned to the other.

For the pain-CBT an MBSR project, participants will be randomized at the group level (ie, pain-CBT, MBSR, WL–pain-CBT, or WL-MBSR) and sequentially assigned to a cohort, based on when they complete their baseline assessment, without participants or assessors knowing the assigned arm. Given that our target treatment group size is 10 to 15 participants, we will allocate up to 18 participants per class to account for participants who fail to show up for treatment and overall attrition.

For the acupuncture project, participants will be randomized to the verum or sham arm using a biased coin algorithm [93], an adaptive randomization process assuring participant similarity between arms in preselected characteristics. For example, each participant will be classified as having less or more extreme baseline pain severity, using 7 out of 10 as a cutoff. For example, the randomization algorithm will automatically adjust the randomization ratio from 50:50 probability of assignment to 40:60, such that a participant with extreme pain will be less likely randomized into the arm that has more participants with extreme pain.

Blinding

Treatment providers will not be blind to treatment allocation and will not be involved in outcome assessment. Assessors will be blind to the treatment arm at pre- and posttreatment, including follow-up assessments. In the acupuncture project, participants will be blinded [89]. In the pain-CBT and MBSR project, participants cannot be blinded to treatment; however, allocation will occur only after baseline measures are completed.

Study Treatments

Pain-CBT will be delivered in group format (10-18 participants) across eight 2-hour weekly sessions by doctoral-level psychologists. Study psychologists will be trained on the pain-CBT study protocol and supervised by BD, a senior psychologist and research team member. The pain-CBT treatment will follow the manualized and validated protocol specifically tailored for chronic low back pain [54,94,95]. It consists of psychoeducation about pain, goal setting, progressive muscle relaxation, activity scheduling, cognitive restructuring of pain cognitions and fear avoidance beliefs, exposure to feared physical activities, relapse prevention, and stress-coping skills. The protocol also provides participants with the following: (1) a participant workbook with relevant worksheets for home and in-class use, (2) two CDs with eight guided relaxation and

imagery exercises for home use, and (3) Turk and Winter's book, The Pain Survival Guide [96], for optional reading (see Table 3 for in-class curriculum details).

MBSR will be delivered in a similar group format (10-18 participants) by a certified instructor with extensive experience delivering MBSR in clinical trials. MBSR will consist of 10 sessions, including an introductory session, eight 2.5-hour weekly sessions, and an optional 1-day meditation retreat. MBSR consists of informal and formal mindful meditation exercises practiced in class and at home. Each class consists of guided meditations, gentle movement exercises, lectures, and group discussions. The course includes a daylong retreat weekend session (Table 4) within the last 3 weeks. Between classes, students engage in home practice through meditation CDs, homework assignments, and readings from the course textbook, Full Catastrophe Living by Kabat-Zinn and Hanh [97]. All participants will be provided with two meditation CDs, Full Catastrophe Living, and handouts for homework assignments (see Table 3 for in-class curriculum details).

Participants in the WL arms will undergo no intervention for 8 weeks and then be assigned to pain-CBT or MBSR, according to availability. The initial 8 weeks of the WL condition will provide control for habituation to the assessments and for nonspecific factors, such as self-monitoring and contact with the research team.

Table 3. Pain-CBT[a] and MBSR[b,c] in-class curriculum.

Session No.	Pain-CBT curriculum	MBSR curriculum
1	Welcome and introductions, including group rules, logistics, etc; CBT rationale; pain physiotherapy; relaxation rationale; importance of home practice; and diaphragmatic breathing	Introduction to program, foundations of mindfulness, more right with you than wrong, and introduction to body scan meditation
2	Goal setting, activation, and pacing (SMART[d], rest-activity cycle, etc); red flags; coping with flare-ups and creating a flare-up plan; and 7-muscle group PMR[e]	Patience, working with perceptions, the wandering mind, and the STOP[f] exercise
3	Role of thoughts and feelings in pain, introduction to CBT and terms, introduction to 3-column thought record, and 4-muscle group PMR	Nonstriving, introduction to awareness of breathing meditation, mindful lying yoga, and attention vs disattention
4	Evaluating and generating alternate thoughts, introduction to evidence gathering, introduction to 4-column thought record, and 4-muscle group PMR, no tension	Nonjudging, responding vs reacting, seeing our patterns, sitting meditation, standing yoga, and research on stress and stress hardiness
5	More on evidence gathering and alternate thoughts (more detail), working with thoughts review, and body scan	Acknowledgment, group reflections on halfway point, small and large groups, sitting meditation, and Qi Gong
6	Thought records review and walking body scan	Letting it be, skillful communication, avoiding difficulty vs entering and blending, lovingkindness meditation, and walking meditation
7	Review of skills, troubleshooting regarding thought records, pain and mood, pain core beliefs, and sleep tips	Sitting meditation, mindful movement, trust and self-reliance, learning how to practice on one's own, and mindfulness in everyday life
8	Review of skills, "signs" of not using skills: creating a plan for maintaining gains and dealing with setbacks, termination and wrap-up, and guided imagery	Sitting meditation, mindful movement, the class never ends: practice for the rest of your life, and course review and group reflection

[a]CBT: cognitive behavioral therapy.

[b]MSBR: mindfulness-based stress reduction.

[c]The MBSR curriculum also includes an orientation pre-MBSR session and the daylong retreat.

[d]SMART: Specific, Measurable, Achievable, Realistic, and Time-bound.

[e]PMR: progressive muscle relaxation.

[f]STOP: Stop, Take a breath, Observe, Proceed.

Table 4. Outline of mindfulness-based stress reduction group's daylong retreat.

Time	Activity
9:30 AM	Introductions
10 AM	Awareness of breathing
10:15 AM	Lying yoga
10:30 AM	Body scan meditation
11:15 AM	Walking meditation
11:45 AM	Sitting meditation
12:15 PM	Lunch and rest
1:30 PM	Yoga
2 PM	Sitting meditation
2:30 PM	Walking meditation
2:45 PM	Sitting meditation
3:10 PM	Walking meditation
3:25 PM	Lovingkindness meditation
3:45 PM	Group discussion (check out)
4:10 PM	Farewell

A licensed acupuncturist will deliver both real and sham electroacupuncture over an 8-week period and 16 sessions. Treatment will consist of standardized electroacupuncture administration, both in terms of point selection and stimulation level. Each session will last approximately 45 minutes, except the first session, which will last 90 minutes and include an initial clinical assessment by the acupuncturist. The real electroacupuncture session will include the use of 20 needles per session. Flexibility in point selection is built into the standardized electroacupuncture protocol to allow for up to 10 more needles in cases where the patient reports hip or buttock pain or if the patient does not experience at least 30% pain reduction after the first four sessions. The sham electroacupuncture will include the use of nonpenetrating needles [98] at non–meridian points (ie, away from the center of the back) to minimize potential physiological effects, and since previous studies indicated potential pain relief attributed to nonpenetrating touch at the location of pain [99,100]. As previously implemented [101], sham electroacupuncture will be conducted by connecting broken wires to the electrical stimulators. The full protocol describing acupuncturist selection and training as well as treatment parameters, including point selection and location, has been published [89].

Treatment Fidelity

The manualized treatment protocols in pain-CBT and MBSR provide structured content for every treatment session, with little room for therapist drift. To further ensure treatment fidelity, a checklist was created for each session of both treatments. These fidelity checklists contain the essential components of the respective treatment session. Treatment fidelity ratings will be conducted in real time during each pain-CBT or MBSR session by a trained research specialist familiar with the treatment they are rating. Each treatment provider is given the criteria that will be used for treatment fidelity.

For acupuncture, treatment fidelity ratings will be based on reviews of structured case report forms completed by the acupuncturists after each session and audio session recordings. The review will include a random sample of 10% to 15% of sessions provided to participants seen by each acupuncturist. To minimize potential drift from treatment protocol and optimize fidelity, there will be quarterly meetings of the acupuncturists with JTK, who has extensive experience in delivering electroacupuncture for pain. During these meetings, corrective feedback of protocol deviations will be discussed, as needed.

Data Collection, Management, and Quality Control

Table 5 [92,102-127] summarizes the questionnaires, domains assessed, and timing of administration. All questionnaires will be completed via a Health Insurance Portability and Accountability Act–compliant REDCap platform. Participants will receive email reminders to complete their surveys via a secure link. Participants will also undergo physical assessment, quantitative sensory testing, and neuroimaging at pre- and posttreatment. The research team will assess data quality every 6 months by plotting data range and checking for missing values on REDCap, without unblinding the treatment assignment. Adherence and retention will be promoted by appointment reminders through email, text, and phone the day before scheduled assessments. In these reminders, we communicate the expectation and importance of attending all intervention and assessment visits. Participant compensation is contingent on the number of sessions they complete.

Table 5. Schedule of measures administration.

Measurement	Pretreatment		Treatment (8 weeks)	Posttreatment	Follow-up month					Longitudinal surveys[a]
	Screening	Baseline			1	3	6	9	12	
Demographics	✓[b]									
Medical history	✓									
Mini–International Neuropsychiatric Interview [92]	✓									
Childhood Trauma Questionnaire [102]		✓								
Marlowe-Crowne Social Desirability Scale [103]		✓								
Stanford Expectations of Treatment Scale [104]			✓							
Response Style Questionnaire [105]		✓		✓						
Trait Meta Mood Scale and Toronto Alexithymia Scale hybrid [106]		✓		✓						
Credibility Expectancy Questionnaire [107]				✓						
Satisfaction with treatment[c]				✓						
Working Alliance Inventory [108]				✓						
Daily questionnaire[d]		✓	✓	✓						
Anxiety Sensitivity Index [109]		✓		✓			✓		✓	
Attentional Control Scale [110]		✓		✓			✓		✓	
Cognitive Distortions Questionnaire [111]		✓		✓			✓		✓	
Emotion Regulation Questionnaire [112]		✓		✓		✓	✓	✓	✓	
Five-Facet Mindfulness Questionnaire [113]		✓		✓		✓	✓	✓	✓	
Implicit Theories of Emotion Scale [114]		✓		✓		✓	✓	✓	✓	
Positive and Negative Affect Schedule [115]		✓		✓		✓	✓	✓	✓	
Short-form McGill Pain Questionnaire [116]		✓		✓		✓	✓	✓	✓	
Patient Global Impression of Change [117]				✓		✓	✓	✓	✓	
Weekly questionnaire[e]			✓		✓	✓	✓	✓	✓	
Sleep bruxism[c]		✓		✓		✓	✓	✓	✓	
Body pain map [118]		✓		✓		✓	✓	✓	✓	✓
NIH[f] PROMIS[g] [119] (mobility, social isolation, and upper-extremity scales)				✓	✓	✓	✓	✓	✓	✓
NIH PROMIS (anger, anxiety, depression, fatigue, pain behavior, pain intensity, pain interference, physical function, sleep disturbance, and sleep impairment scales)		✓		✓		✓	✓	✓	✓	✓
Back pain bothersomeness[c]		✓		✓		✓	✓	✓	✓	✓
Chronic Pain Acceptance Questionnaire [120]		✓		✓		✓	✓	✓	✓	✓
Fear-Avoidance Belief Questionnaire [121]		✓		✓		✓	✓	✓	✓	✓
Pain interference with sexual activities		✓		✓		✓	✓	✓	✓	✓
Pain Catastrophizing Scale [122]		✓		✓		✓	✓	✓	✓	✓
Pain Self-Efficacy Questionnaire [123]		✓		✓		✓	✓	✓	✓	✓
Perceived Stress Scale [124]		✓		✓		✓	✓	✓	✓	✓
Roland-Morris Disability Questionnaire [125]		✓		✓		✓	✓	✓	✓	✓
Self-esteem[c]		✓		✓		✓	✓	✓	✓	✓
Satisfaction with Life Scale [126]		✓		✓		✓	✓	✓	✓	✓

Measurement	Pretreatment		Treatment (8 weeks)	Posttreatment	Follow-up month					Longitudinal surveys[a]
	Screening	Baseline			1	3	6	9	12	
NIH PROMIS (global health scale)		✓				✓				✓

[a]Longitudinal surveys will be administered to participants who have been discontinued or withdrawn from the study. These questionnaires will be delivered electronically at 2 weeks and at 1, 2, 3, 6, and 12 months following the completion of their baseline behavioral appointment.

[b]A checkmark indicates that the measure was administered at the indicated time point.

[c]This is a single-item measure.

[d]The daily questionnaire consisted of several single items assessing pain severity, various physical health factors, and emotional coping. The questionnaire was administered in 2-week periods at baseline, at the beginning of weeks 1 and 3 of treatment, and posttreatment.

[e]The weekly questionnaire consisted of a combination of the following validated measures: Five-Facet Mindfulness Questionnaire; Pain Catastrophizing Scale; Working Alliance Inventory; Pain Self-Efficacy Questionnaire; Fear-Avoidance Belief Questionnaire; PROMIS pain intensity, fatigue, sleep disturbance, sleep interference, depression, anxiety, and anger scales; Behavioral Activation for Depression Scale (short form) [127]; Chronic Pain Acceptance Questionnaire; and Positive and Negative Affect Schedule. Measures for assessing frequency and capability of using cognitive and attention regulation to modulate back pain were included, in addition to single-item questions on pain intensity and relaxation.

[f]NIH: National Institutes of Health.

[g]PROMIS: Patient-Reported Outcomes Measurement Information System.

Physical Assessment

Various behavioral tasks will assess objective physical functioning [128,129]. The tasks include measures of forward-bending range of motion, sit-to-stand speed, single-leg balance, back muscle endurance, 10-meter walking speed, and 2-minute walking endurance. Trained staff administer the tests and document participant performance.

Quantitative Sensory Testing

A two-point discrimination task measures participant's tactile acuity via an established protocol [130]. Using a dolorimeter (FDK-10; Wagner Instruments), pressure pain threshold and tolerance will be measured at the bilateral trapezius muscle bed, thumb nail beds, and lumbar regions (1-inch lateral to midline of L4-L5 interspinous space, because participants tend to be more sensitive in the low back). Pain threshold, tolerance, and curve response to thermal heat pain will be measured using a Medoc Pathway machine (Ramat Ishay). Testing tasks will proceed from the least to most stimulating. The test location is initially on the left hand over the thenar eminence and rotated to the opposite hand for each subsequent thermal testing. Although different in location, our methods for obtaining the blunt pressure and thermal sensitivity measures are similar to the German Research Network on Neuropathic Pain protocol [131]. Based on our lab's published protocol [132], dynamic quantitative sensory testing, including thermal temporal summation and followed by conditioned pain modulation, will conclude the sensory testing module.

Neuroimaging

Most chronic low back pain participants will undergo two MRI scans of their brain: one pretreatment and one posttreatment. Participants allocated to the WL group will undergo three scans: before the waiting period, after the waiting period, and after the subsequent delivered treatment. The healthy control group will undergo one scan only as a baseline comparison to the pretreatment and pre-WL scans in the chronic low back pain group.

The brain scans will include structural and functional neuroimaging protocols. Structural scans include high-resolution gray and white matter scans. Functional scans will include a 10-minute resting-state scan and a heat-pain regulation task. This task is an experimental paradigm using heat as an evoked pain stimulus, applied to the low back. Prior to the scan, participants are trained in cognitive regulation and attention regulation, which will be implemented during evoked pain inside the scanner. While in the scanner, participants are presented with visual cues on a screen instructing them to respond to a 10-second heat stimulus in three different ways. The *respond* cue (ie, pain reaction) instructs participants to focus on the pain and allow their mind to react to the pain normally. The *reframe* cue (ie, cognitive regulation) instructs participants to reinterpret the way they think about the heat stimulus to reduce their negative reactivity to the pain. The *observe* cue (ie, attention regulation) instructs participants to observe and attend all aspects of their overall experience and to try not to focus on anything in particular. A fourth condition, *rest* (ie, no pain), serves as a baseline control and is not paired with a heat stimulus. After each heat stimulus, participants will rate their pain intensity and unpleasantness with a button box on a visual analogue scale ranging from 0 ("no pain") to 10 ("worst imaginable pain"). The functional MRI heat-pain regulation task consists of a random sequence of the four conditions (10 trials per condition; no condition permitted to occur more than twice in a row) over 17.5 minutes. Though participants are instructed that each temperature may be the same or different than the one before, each heat stimulus is the same temperature: a pain intensity rating of approximately 6 out of 10 as determined by a fine thresholding procedure prior to scanning with each individual participant.

Standard analytic approaches will be used to preprocess and analyze the neuroimaging data, using common software packages, such as FSL, SPM, or both. The steps and algorithms of such software continue to improve, so the precise approach will be determined upon completion of data accrual. However, we anticipate that the general approaches will be similar to those of previously published methods [17,84,133-135]. For example, analysis of structural data may include probabilistic tissue

segmentation, rigid co-registration for detecting within-individual differences, and high-dimensional normalization for establishing between-subject differences [134]. Preprocessing and analysis of functional data will most probably include head motion correction, spatial smoothing, high-pass temporal filtering, and usage of various general linear models to conduct various comparisons between conditions and groups [84].

Sample Size Determination

We determined sample sizes for both projects to ensure adequate power to detect significant mechanistic differences associated with the treatment comparisons.

Pain-CBT Versus MBSR

To estimate sample size, we conducted power analyses based on effect sizes derived from results from our pilot studies using G*Power (version 3; Heinrich-Heine-Universität Düsseldorf). Behavioral and functional MRI studies resulted in similar medium effect sizes. For Aim 1 (ie, pre- to posttreatment), testing a 2-way interaction in a 3-group (CBT, MBSR, and WL) × 3-time (pretreatment, posttreatment, and 6-month follow-up) repeated-measures analysis of variance (ANOVA) for clinical symptoms and well-being measures, a power of 0.80 can be obtained based on a medium effect (Cohen *d*=0.5), α=.05, and 32 participants per group. For Aim 2 (ie, treatment effect on cognitive regulation and attention regulation), testing a 2-way interaction in a 2-group (CBT and MBSR) × 2-time (pretreatment and posttreatment) repeated-measures ANOVA for negative emotion to evoked pain, a power of 0.80 can be obtained based on a medium effect (Cohen *d*=0.5), α=.05, and 32 participants per group. We anticipate 6 out of 40 (15%) dropped participants for each arm.

Acupuncture: Real Versus Sham

We computed sample size based on detecting differential changes in temporal summation, the primary mediator. Our pilot study suggested an average change of 10 to 25 points of the 100-point visual analogue scale with an SD of 12 following acupuncture. Prior studies suggest no treatment effect in controls receiving sham acupuncture [136]. However, given the imprecision of the pilot study's estimates of effect sizes, we have powered the study to detect a medium effect (*d*=0.56) with 50 participants in each arm, using a 2-tailed test with α=.05 and β=.8. If the point estimates from the pilot prove accurate, this project will be very well powered (98% power) to detect large effects (*d*=0.833). To account for approximately 20% attrition, we will enroll around 120 study participants.

Statistical Considerations

Overview

Below, we outline analyses to address the hypotheses outlined in the original proposal. Given the project's primary focus on mechanisms rather than efficacy, we will perform the primary analyses using longitudinal treatment data with the per-protocol sample. This sample will consist of participants who completed all 3 assessment sessions (ie, pretreatment, posttreatment, and midpoint) and 5 or more out of 8 pain-CBT or MBSR treatments (or ≥13 out of 16 acupuncture visits). During the study and after completion, we will propose additional secondary aims and hypotheses using baseline and longitudinal data on chronic low back pain and before conduct of the analyses. Some of these secondary aims are presented in the Discussion section. Future hypotheses focusing on baseline data will use all available data.

Aims 1 to 3: Pain-CBT Versus MBSR

To address the efficacy aim (Aim 1), we will compute change scores from baseline to *immediately posttreatment* and *6 months posttreatment* for pain severity and well-being. We will conduct paired *t* tests to examine differential between-group changes immediately (CBT vs WL, MBSR vs WL, and CBT vs MBSR) and 6 months posttreatment (CBT vs MBSR). To test whether pain-CBT and MBSR differentially enhance behavioral and neural indices of the ability to implement cognitive regulation and attention regulation during evoked low back pain (Aim 2), we will conduct 2-treatment (CBT and MBSR) × 2-regulation (cognitive regulation and attention regulation) × 2-time (baseline and posttreatment) repeated-measures mixed-effects models and within and between-group *t* tests on (1) pain ratings and (2) neural responses in ventral emotion-generative and dorsal emotion-regulatory brain regions. To test whether changes in cognitive regulation mediate CBT but not MBSR outcomes, and whether changes in attention regulation mediate MBSR but not CBT outcomes (Aim 3), we will implement the MacArthur mediator model. Finally, we will test whether, immediately posttreatment, both CBT and MBSR yield greater improvements in pain symptom severity and well-being in chronic low back pain compared to WL participants. We expect equivalent improvement for MBSR and CBT immediately and 6 months posttreatment. Post-WL participants will enter CBT or MBSR treatment. If between-group *t* tests of immediate versus posttreatment WL-CBT and posttreatment WL-MBSR groups, separately, show no difference in pain symptoms and well-being, then we will use all participants treated with CBT or MBSR to conduct an exploratory moderator analysis to investigate whether any baseline demographic (eg, age and education), clinical (eg, comorbidity, prior treatment, age of onset, and symptom severity), or emotion (eg, depression, anxiety, and affect or trait emotion regulation) variables reliably identify who will benefit from CBT or MBSR.

Aims 4 to 5: Real Versus Sham Acupuncture

To test whether real electroacupuncture versus sham electroacupuncture leads to a greater reduction in temporal summation from baseline to the end of week 4 (Aim 4), we will conduct a 2-tailed, 2-sample *t* test. To test whether reduction in temporal summation from baseline to week 4 mediates reduction in weekly back pain bothersomeness scores (from baseline to posttreatment), we will use a McArthur mediation analysis. We will determine significant treatment effects on the clinical outcome using a mixed-effects model, with weekly back-pain bothersomeness scores as the dependent variable and treatment assignment as the independent variable. We will include a subject-specific intercept to account for within-patient correlations. We will test a second mixed-effects model, with longitudinally measured back-pain bothersomeness scores as the independent variable. Treatment arm, reduction in temporal summation from baseline to week 4, and their interaction will

be independent variables. A significant main effect for change in temporal summation or interaction between change in temporal summation and treatment arm will be evidence of mediation. To test whether participant expectations of benefits predict reduction in back-pain bothersomeness scores (weeks 0-10; Aim 5), we will use a mixed-effects regression analysis with weekly measured back-pain bothersomeness scores as the dependent variable and expectation, treatment assignment, and their interaction as independent variables.

Results

Participant recruitment began on March 17, 2015, and will end in March 2023. Recruitment was halted in March 2020 due to COVID-19 and resumed in December 2021. The trials were registered in ClinicalTrials.gov (NCT02503475) on July 21, 2015. The initial protocols and subsequent revisions follow NCCIH guidelines.

Discussion

This NCCIH CERC P01–funded research strategy represents a novel direction for pain research for investigating common and distinct mechanisms of three mind-body therapies for chronic low back pain. The common and distinct mechanisms of these three mind-body therapies can be elucidated by comparing data across projects sharing phenotyping and data collection systems. While these therapies have been previously studied, the current effort extends them in several more ways. Specifically, we will be focusing on the role of different pain modulatory and emotion regulatory systems (ie, cognitive regulation and attention regulation) and their interactions. Moreover, we use neuroimaging to reveal underlying neural mechanisms that will support the development of biomarkers and neural targets for neuromodulatory techniques. These novel approaches will allow investigators to better delineate the biopsychosocial basis of chronic low back pain and support a personalized approach for treatment efficacy.

Furthermore, the comprehensive approach to systemically phenotyping people with chronic low back pain (expected N>300) will address a wealth of clinically important questions. Our comprehensive, longitudinal data set will represent one of the largest ever collected for chronic low back pain, with the exception of the anticipated deep phenotyping data of chronic low back pain by the NIH Back Pain Consortium several years out. The recruitment of healthy controls (ie, individuals without chronic pain, in general, and without chronic low back pain, specifically) allows investigators to elucidate novel mechanisms that may be unique to chronic low back pain, or that define clinically distinct chronic low back pain subtypes. Indeed, there is significant interest in defining subtypes of chronic pain, and its trajectories, that represent high-impact chronic pain. Additionally, the daily assessment data will provide valuable information on chronic low back pain symptom variability and flares.

Together, these extensive data collection efforts will help address the original overarching study hypotheses (see Methods section) and the following secondary clinically significant aims to advance clinical care for patients with chronic low back pain:

1. Identify biopsychosocial subsets of individuals with chronic low back pain with differing underlying pathogenesis defining their symptom severity, and define a diagnostic biomarker to classify chronic low back pain subtypes.
2. Identify predictive biomarkers using comprehensive baseline patterns of collected biopsychosocial data, combined with brief daily trajectories, to accurately predict treatment responsive to pain-CBT, MBSR, and real or sham acupuncture.
3. Identify differences in baseline and longitudinal emotion regulation characteristics that distinguish baseline characteristics of symptom severity in chronic low back pain and mediate treatment response to mind-body therapies.
4. Identify baseline pretreatment efficacy expectations associated with improved treatment outcomes and with distinctive neural imaging patterns.
5. Characterize symptom flares and mediating information on response to mind-body therapies through daily assessments of pain symptoms, emotional functioning, general health, and expectancy.
6. Determine whether individuals with longer chronic low back pain symptom duration have greater symptom severity, less psychosocial functioning, and different biological mechanisms than those with shorter symptom duration.
7. Determine whether individuals with localized chronic low back pain have different symptoms and underlying pathogenesis than those with chronic overlapping pain conditions and can be clustered based on baseline and longitudinal data.
8. Determine whether adverse childhood experiences are associated with greater symptom severity and decreased quality of life in individuals with chronic low back pain.
9. Determine whether various demographic factors, such as sex differences, ethnic background, and socioeconomic status, can distinguish baseline and longitudinal trajectories of symptom severity, neural mechanisms, and treatment responsiveness.

Results from these studies will advance our understanding of the pathophysiology and clinical characteristics of chronic low back pain, elucidate the mechanisms responsible for treatment response to mind-body therapies, and improve future clinical efforts for risk and treatment stratification to optimize care for individuals suffering from chronic low back pain.

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AT008477 [J-TK]), the National Institute on Drug Abuse (NIDA; grants K24 DA029262 [SM] and K24 DA053564 [BD]), the National Institute of Neurological Disorders and Stroke (grant K24 NS126781 [SM]), the NIDA (grant T32 DA035165 [SM]), and the Redlich Pain Endowment (SM). All statements in this report are solely those of the authors and do not necessarily represent the views of the National Institutes of Health (NIH).

Conflicts of Interest

BD is Chief Science Advisor at AppliedVR, and her consulting role with this company (personal fees) is unrelated to the current work. BD receives royalties for four pain treatment books she has authored or coauthored. She is the principal investigator for pain research awards from the Patient-Centered Research Outcomes Research Institute and the National Institutes of Health (NIH) that investigate cognitive behavioral therapy (CBT) for chronic pain. BD serves on the Board of Directors for the American Academy of Pain Medicine and is on the Board of Directors for the Institute for Brain Potential. BD is a scientific member of the NIH Interagency Pain Research Coordinating Committee, a former member of the Centers for Disease Control and Prevention Opioid Workgroup (2020-2021), a former scientific advisory board member of the National Pain Advocacy Center (2021-2022), a current member of the Pain Advisory Group of the American Psychological Association, and serves on the Medical Advisory Board for the Facial Pain Association.

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Abbreviations

ANOVA: analysis of variance
CBT: cognitive behavioral therapy
CERC: Center of Excellence for Research on Complementary and Alternative Medicine
MBSR: mindfulness-based stress reduction
MRI: magnetic resonance imaging
NCCIH: National Center for Complementary and Integrative Health
NIDA: National Institute on Drug Abuse
NIH: National Institutes of Health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
WL: wait-list

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Protocol

Therapist-Delivered Versus Care Ally–Assisted Massage for Veterans With Chronic Neck Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic neck pain (CNP) is prevalent, and it reduces functional status and quality of life and is associated with deleterious psychological outcomes in affected individuals. Despite the desirability of massage and its demonstrated effectiveness in CNP treatment, multiple accessibility barriers exist. Caregiver-applied massage has demonstrated feasibility in various populations but has not been examined in Veterans with CNP or compared in parallel to therapist-delivered massage.

Objective: This manuscript described the original study design, lessons learned, and resultant design modifications for the Trial Outcomes for Massage: Care Ally–Assisted Versus Therapist-Treated (TOMCATT) study.

Methods: TOMCATT began as a 3-arm, randomized controlled trial of 2 massage delivery approaches for Veterans with CNP with measures collected at baseline, 1 and 3 months after intervention, and 6 months (follow-up). Arm I, care ally–assisted massage, consisted of an in-person, 3.5-hour training workshop, an instructional DVD, a printed treatment manual, and three 30-minute at-home care ally–assisted massage sessions weekly for 3 months. Arm II, therapist-treated massage, consisted of two 60-minute sessions tailored to individual pain experiences and treatments per week for 3 months. The treatments followed a standardized Swedish massage approach. Arm III consisted of wait-list control.

Results: Retention and engagement challenges in the first 30 months were significant in the care ally–assisted massage study arm (63% attrition between randomization and treatment initiation) and prompted modification to a 2-arm trial, that is, removing arm I.

Conclusions: The modified TOMCATT study successfully launched and exceeded recruitment goals 2.5 months before the necessary COVID-19 pause and is expected to be completed by early 2023.

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KEYWORDS

Veterans; chronic neck pain; integrative medicine; whole health; modified trial design; therapist-delivered versus care ally–assisted massage for Veterans with chronic neck pain; TOMCATT

Introduction

Background

Neck pain is common in adults aged >50 years and is the fourth leading cause of disability in the United States [1]. Chronic neck pain (CNP) reduces functional status and quality of life and is associated with deleterious psychological outcomes in affected individuals. CNP accounts for more than 10 million ambulatory medical visits per year [2].

Medications are most commonly used to treat CNP in clinical practice; however, systematic reviews find limited evidence for effective treatments relative to low back pain, and current therapies show only modest effect sizes [3]. Because medications and other conventional treatments often fail to substantially relieve pain, patients frequently seek other treatments.

In all, 58% of the older adults surveyed used some type of alternative treatment [4], and pain is the primary reason individuals use complementary treatments [5]. After low back pain, CNP is the most common pain condition for complementary health use [6]. Massage is the second (after chiropractic) most commonly used complementary treatment for CNP [7]. Studies have shown that massage is safe, with few risks and rare serious adverse effects [8,9].

Despite its safety and potential benefits, the expense associated with massage therapy limits its accessibility. Teaching informal care allies to provide massages has the potential to improve accessibility. Kozak et al [10] demonstrated the feasibility of caregiver-delivered massage, which led to significant decreases in pain, stress or anxiety, and fatigue in Veterans with cancer. Collinge et al [11] recruited 97 patient or caregiver dyads to practice massage for individuals experiencing cancer. Caregiver-applied interventions led to decreases in patients' pain, depression, and other cancer-related symptoms [11]. Although the feasibility and benefit of the care ally–applied massage approach have been established in cancer populations, it has not been examined specifically in non–cancer-related musculoskeletal pain populations.

The Trial Outcomes for Massage: Care Ally–Assisted Versus Therapist-Treated (TOMCATT) study began as a 3-arm, randomized controlled trial of 2 massage therapy delivery approaches for CNP. The primary aim of this study was to compare care ally–assisted massage (CA-M) and therapist-treated massage (TT-M) with a wait-list control group (WL-C) for pain-related disability. The secondary outcomes included pain severity, health-related quality of life, depression, anxiety, and stress. Before pausing the TOMCATT activities due to the COVID-19 pandemic, the study design was modified to a 2-arm study. The CA-M arm was discontinued owing to recruitment and adherence challenges.

Objectives

The primary purpose of this manuscript is to describe the original TOMCATT study design, the challenges faced during the study's first 2 years of recruitment, and the resultant design modification to a 2-arm study. Specifically, we describe the original TOMCATT methodology, materials, and procedures in the Methods section and report the initial enrollment and intervention initiation outcomes for the first 30 recruitment months, rationale for the modified study design, and subsequent modified TOMCATT methodology in the Results section. TOMCATT is an active study that has restarted from the COVID-19–related pause and is projected to be concluded by early 2023.

Methods

Overall Original Design

TOMCATT's study population consisted of Veterans with CNP randomized to one of 3 study arms: CA-M, TT-M, or WL-C. All eligible patients had an identified care ally, but only those randomized to the CA-M arm ultimately participated in TOMCATT with their care ally. Those randomized to the CA-M arm attended a group training workshop that taught them a massage routine. After the training, CA-M dyads were asked to complete the learned 30-minute massage routine 3 times per week for 12 weeks and document the massages that were delivered in a log. The TT-M intervention consists of twice weekly, hour-long massage sessions provided by massage therapists trained to deliver semistandardized, individualized treatments.

TOMCATT outcome assessments were conducted via interviews at baseline and 1, 3, and 6 months in all study arms. The primary outcomes were neck pain and related disabilities. The secondary outcomes were other pain measures, health-related quality of life, depression, anxiety, and pain cognition.

Ethics Approval

TOMCATT was reviewed and approved by the Indiana University Institutional Review Board (#1604689005_9034) and Veterans Administration Research Review Committee (VA project ID:IIR 15-333) and registered with ClinicalTrials.gov (NCT03100539). All participants engaged in a one-on-one informed consent process with the study personnel and provided written informed consent.

Eligibility

Veterans are eligible if they meet criteria outlined in Textbox 1.

Textbox 1. Trial Outcomes for Massage: Care Ally–Assisted Versus Therapist-Treated study eligibility criteria.

Inclusion criteria

- Aged at least 18 years
- Chronic neck pain for ≥6 months
- At least moderate disability per the Neck Disability Index (score of ≥10)
- Access to a working telephone
- Ability and willingness to attend 2 treatments per week for 12 weeks
- Have a care ally (spouse, partner, family member, or friend) willing to learn and provide message therapy during the study period

Exclusion criteria

- Neck pain secondary to vertebral fracture or metastatic cancer
- Complex neck pain (eg, cervical radiculopathy)
- Any professional massage therapy within the last 6 months excluding as part of physical therapy, or visit to the chiropractor or hairdresser
- Potential contraindication to massage (eg, hypersensitivity to touch)
- Hospitalized for psychiatric reasons in the last 3 months
- Occurrence of stroke, transient ischemic attack, heart attack, cervical injury such as whiplash, or hospitalization for chronic obstructive pulmonary disease, emphysema, or congestive heart failure within 6 months of enrollment
- Active suicidal ideation
- Moderate to severe cognitive impairment
- Pending neck surgery
- Involvement in ongoing pain trial or massage study

Eligible Veterans who provided written informed consent were enrolled and underwent a baseline assessment. Randomized care allies also provided written consent to participate at the beginning of the intervention workshop training. Care allies were eligible if their *partnered* Veteran was randomized to the care ally arm, they attended the CA-M training workshop with their Veteran partner and did not have medical concerns that might interfere with giving a massage.

Recruitment

Primary care providers at the Roudebush Veterans Affairs (VA) Medical Center in Indianapolis, Indiana, and surrounding community-based outpatient clinics were informed of the TOMCATT study details and asked to provide signed approval for the research team to contact their patients for possible study participation. Potential participants were identified by querying the VA's electronic medical record to create a master list of Veterans meeting the following criteria: (1) neck pain diagnoses per International Classification of Diseases, Ninth Revision codes 721.0 to 723.9 and (2) primary care clinic visits in the past year (a proxy measure of VA care engagement).

A recruitment letter signed by their provider is mailed to qualifying Veterans to describe the study. Letters contain an initial screening for neck pain–related disability that interested Veterans may return if they would like to be contacted to assess their eligibility and possible participation. An appointment is scheduled for eligible Veterans to sign an informed consent statement and the Health Insurance Portability and Accountability Act authorization for those indicating a desire to participate. Baseline interviews and assessments are conducted by a research assistant (MK, EE, or BL) before randomization to minimize ascertainment bias. Veterans also self-identified as being interested in study participation after learning of TOMCATT through acquaintances, word of mouth, or study pamphlets.

Randomization

Patients were initially assigned to one of the three study arms (TT-M, CA-M, and WL-C) using randomization lists created by the study statistician. Stratified block randomization, with random block sizes of 3 and 6, was used for the original plan to enroll 468 participants (excluding care allies enrolled within the CA-M arm). Sex (male or female) was the only randomization strata used.

Data Collection Protocol

Table 1 and Table 2 outline the data collection protocol for the Veteran and care ally participants, respectively. Veteran and care ally participants in the CA-M arm also completed a brief learning objectives survey following the training workshop.

Table 1. Veteran participant data collection protocol.

Domain	Measure	Items, n	0 months	1 month	3 months	6 months
Demographics	Demographics; disability compensation; comorbidity	36	✓			
Medical comorbidity	Checklist of common medical or psychological conditions		✓			
Neck pain disability	Neck Disability Index [12]	10	✓	✓	✓	✓
Pain severity	Brief Pain Inventory [13]	11	✓	✓	✓	✓
Pain interference	PROMIS[a]-pain [14]	4	✓	✓	✓	✓
Psychological	PHQ[b]-9-depression [15]	9	✓		✓	✓
Psychological	PROMIS-depression [16]	9	✓		✓	✓
Psychological	GAD[c]-7-anxiety [17]	7	✓		✓	✓
Psychological	Veterans Affairs PTSD[d] screener [18]	4	✓		✓	
Psychological	PTSD-PCL[e]-17 [19]	17	✓		✓	
Psychological	Perceived stress scale [20]	10	✓		✓	
Generic HRQL[f]	MOS-VR[g]-36 [21]	36	✓	✓	✓	✓
Sleep	MOS-Sleep Scale [22]	12	✓		✓	
Somatic	Somatic Symptom Scale-8 [23]	8	✓		✓	✓
Somatic	SSD[h]-12 [24]	12	✓		✓	✓
Pain beliefs	Pain Catastrophizing Scale [25]	10	✓		✓	
Social support	Multidimensional Scale of Perceived Social Support [26]	12	✓		✓	
Treatment satisfaction	Pain-specific satisfaction [27]	3	✓		✓	✓
Intervention credibility	EXPECT[i] Questionnaire [28]	4	✓		✓	

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]PHQ: Patient Health Questionnaire.

[c]GAD: General Anxiety Disorder.

[d]PTSD: posttraumatic stress disorder.

[e]PCL: posttraumatic checklist.

[f]HRQL: Health-Related Quality of Life.

[g]MOS-VR: Medical Outcomes Study-Veteran version.

[h]SSD: somatic symptom disorder.

[i]EXPECT: Expectations for Complementary and Alternative Medicine Treatments.

Table 2. Care-ally participant data collection protocol.

Domain or measure	Time taken to complete (minutes)	Items, n	0 months	1 month	3 months	6 months
Expectations	1	3	✓		✓	
Brief Pain Inventory [13]	1	3	✓		✓	
PHQ[a]-Stressor Scale	3	9	✓		✓	
PHQ-2-depression	1	2	✓		✓	
GAD[b]-2-anxiety	1	2	✓		✓	
Care ally burden	3	8	✓		✓	

[a]PHQ: Patient Health Questionnaire.

[b]GAD: General Anxiety Disorder.

Participant Incentives

Veteran participants were reimbursed US $25 per completed outcome assessment, with 4 scheduled assessments (baseline and 1, 3, and 6 months). Participants in the TT-M and WL-C arms were invited to receive all CA-M training and materials after their 6-month interview. Veterans randomized to WL-C are invited to receive a massage from one of the TOMCATT massage therapists. Care allies received a US $50 gift card at the completion of the care ally training and a complimentary massage session.

Interventions

CA-M Intervention

Overview

The CA-M intervention consisted of three components: (1) an in-person training workshop led by NM (coinvestigator and licensed massage therapist), (2) an instructional DVD to reinforce the taught concepts, and (3) a printed treatment manual with illustrations and images from workshop materials. Participants were asked to engage in at least three 30-minute CA-M sessions every week at home for the 3-month intervention period. To standardize the delivery and facilitate reproducibility, the content and general structure of the CA-M routine were taught during the workshop. The DVD included a real-time demonstration of the routine for participants to play during applications if desired. Participants were asked to document their massage activities in a study log and return the log sheets monthly.

CA-M Routine

The CA-M routine consisted of 13 progressive components ordered to reflect logical seated treatment progression and partially followed the therapist-applied treatment progression from the TT-M arm of the study. Participants were asked to follow the general routine flow and time per area allotments outlined in the protocol and to individualize their massages using the learned techniques. Table 3 displays routine specifics and was included for participants in the treatment manual provided during the workshop.

Table 3. The care ally–assisted treatment component, progression, and timing details.

Routine component	Time allotment (minutes)	Component ends at countdown minute	Veteran component activity	Care ally component activity	Accumulated minutes at component's end
Grounding	1	29:00	Deep breathing and self-grounding and centering	Deep breathing and self-grounding and centering	1
Lymph address	2	27:00	Self-provided lymph drainage	Breathing, grounding, and observing; self-lymph drainage	3
Range of motion	1	26:00	Head, neck, shoulder, and upper back movement	Neck, arms, wrists, hands, and shoulders	4
Check-in or initial connection	1	25:00	Receive and provide feedback	Laying on of hands, making connection, and assessing the tissue with gentle touch	5
Stretching	3	22:00	Receive and apply	Apply to partner and self	8
Warming of neck tissue	2	20:00	Receive and give feedback	Gliding strokes to neck and shoulders	10
More specific neck work	3	17:00	Receive and give feedback	Kneading and point work: neck and shoulders	13
Back work and abdomen	3	14:00	Receive and give feedback and self-apply ab work	Compression, point work, and gliding strokes for upper or lower back	16
Shoulders, neck, and scalp	3	11:00	Receive and give feedback	Apply as continuation of above; add scalp	19
Arms and pecs	3	8:00	Receive and give feedback	Apply to both sides through hands	22
Back, shoulders, neck, and scalp	3	5:00	Receive and give feedback	Final specific work and additional attention items	25
Veteran applied specific point work	4	1:00	Self-apply deep back and front of the neck work	Observe or self-apply	29
Final "sweep" and closure	1	0:00	Receive	Compression, effleurage, gentle tissue movement, or stretching and closure	30

CA-M Workshop Specifics

Participant dyads (Veteran and care ally) randomized to CA-M were scheduled to attend a single 3- to 4-hour (including breaks) in-person training workshop held at the Roudebush VA Medical Center. In all, 1-7 dyads (2-14 individuals) attended training workshops. Each training workshop consisted of six parts: (1) introductions and objectives; (2) general instruction (via lecture) on massage, communication approach, safety, CNP, and trigger points that may exacerbate neck pain; (3) massage technique demonstration and supervised practice; (4) specific self-care aspects of the routine and additional and individualized trigger point treatment strategies; (5) demonstration and practice of standardized care ally–assisted massage routine; and (6) questions, closure, and wrap-up.

NM conducted training that demonstrated and encouraged the safe performance of massage tailored to the participants' needs and abilities. Basic Swedish massage techniques (eg, effleurage [identified as gliding strokes to participants], petrissage [identified as kneading to participants], and compression) were taught during the training, as well as how to use the training DVD and accompanying workbook given to participants. The levels for depth of touch were quantified from very light to so deep that they were not used and described based on tissue-level engagement intention and visual cues from applicant fingertips and recipient skin.

CA-M: Instructional DVD Specifics

The TOMCATT DVD comprised 5 sections that highlight NM discussing key aspects of the massage routine and workshop-taught techniques. In addition, the DVD included a real-time, full demonstration moving from start to finish through the 30-minute care ally–assisted massage routine. Dyads were encouraged to use the DVD to review technique and positioning instructions and to guide each of the 3 weekly applications of the routine to help with timing and treatment fidelity and to reinforce learning objectives. The DVD main menu (Figure 1) provided viewers with the options to play and view the following choices: (1) the massage routine demonstration only; (2) an introduction from the study principal investigator (MJB), instruction on how to document adherence and compliance to care ally–assisted massage protocol and application, and contact information; (3) instruction and supplemental information or reminders related to how to set up a treatment space within the home, Veteran positioning, and care ally body mechanics during treatment; (4) instruction and supportive reminders regarding massage techniques and how to apply learned techniques to the various body regions (eg, shoulders and arms) addressed in the routine; and (5) review instruction of techniques and concepts learned during the workshop.

Training workshop attendees were also taught how to use the study developed and provided training DVD and an accompanying workbook. The training DVD was a professionally produced, multisectioned DVD designed to complement and reinforce the techniques learned during the training workshop. One section of the DVD was a real-time, full demonstration moving from start to finish through the 30-minute, care ally–assisted massage routine.

Figure 1. Instructional DVD main menu.

CA-M: Treatment Manual Specifics

The CA-M treatment manual is a 32-page, full-color, spiral-bound reference for material taught in the training workshop. The manual content included slides from the training and content arranged to mirror the progression of the training. The manual contained images of associated referral pain patterns, trigger point locations, and treatment of particular trigger points. The treatment manual was given to the participant dyads at the beginning of the CA-M training workshop and had space within it for participants to take notes during the training and use regularly during the study activity as a reference.

CA-M: Adherence

Attempts were made to boost adherence and provide posttraining support to participants. Study personnel contacted Veterans and care allies at 2 weeks and in months 2 and 4 to inquire about any barriers to home massage (eg, care ally fatigue or burden,

challenges with learning massage techniques and routine, and difficulty adhering to 30-minute sessions). For adherence monitoring, participants were asked to track their use of the DVD and record the time spent on massage on a log form. Monthly log returns were made using postage-paid and addressed envelopes.

TT-M Intervention

Overview

The TT-M intervention delivery protocol was based on prior research and standardized by treatment intention ordering reflective of typical treatments within therapeutic massage practice for specific pain [29-31]. A Swedish massage–based protocol was chosen because it encompasses the most widely taught and practiced massage techniques that are well-defined procedurally. The allowable techniques included effleurage, petrissage, friction, myofascial, stretching, proprioceptive neuromuscular facilitation, muscle energy technique, stretching, trigger point, compression, rocking, and craniosacral therapy. The specified techniques and activities prohibited by the protocol were deep pressure applied to the anterior neck, movement re-education, shiatsu, and energy work such as Reiki. All massage sessions were delivered in a private treatment room at the medical center.

TT-M Protocol

The massage sessions involved a short intake interview followed by 60 minutes of hands-on table time and occurred twice a week (a frequency that balances practicality and efficacy) for 3 months. During the first session, the massage therapist provided an introduction and overview of massage. Thereafter, the TT-M intervention involved a standardized 9-component sequence (Table 4), each with a designated time range that begins with the recipient supine on the massage table. Therapists were instructed to refrain from providing self-care recommendations regarding postures, behavior changes, and sleep.

Table 4. The therapist-treated massage protocol details.

Protocol	Time allotment range (minutes)	Description
Range of motion and assessment	3	Hands-on assessment with participant supine on the massage table including active, passive, and resistive range of motion observation and comfort-related dialogue.
Lymph drainage	2-4	Gentle and light touch techniques were applied to the anterior and lateral neck surface, clavicular area, and upper chest and shoulders to encourage lymphatic stimulation and drainage. The techniques mirrored those taught for self-application in the care ally–assisted massage study arm.
Palpation, tissue assessment, and warm-up	1-2	Hands-on gentle palpation, general assessment, and gliding strokes applied to the neck and shoulders were intended to apply massage cream and warm up the tissue.
Specific neck work I	13-22	The massage session progresses to using Swedish massage techniques including stretching applied on participants supine and focused specifically on the base of the skull, neck, shoulders, and upper back (C1-approximately T3) with the intention to address specific muscles and muscle groupings potentially contributing to the pain presentation.
Compensatory patterns and additional concern areas	15-24	Specific work is performed on other areas of the body potentially impacted by or contributing to the participant's neck pain experience. The participant may change from a supine position to a prone or side-lying position. The arms, back, torso, and legs may all be addressed during this time.
Integration I	7-15	The integration components of the protocol are intended to allow the body an opportunity to incorporate and assimilate tissue changes from the treatment's specific massage work during the "Specific Neck Work and Compensatory Patterns" components. The recommended and used massage techniques to facilitate work integration included craniosacral techniques; gentle rocking; and long, slow, gliding strokes. The intention here is to also allow the body to "connect" back together once specific areas have had focused attention and other areas perhaps have had little to no attention. Integration components can be applied to participants either prone, supine, or side-lying positions.
Specific neck work II	6-10	A second round of specific neck work near the end of the treatment provides additional time to focus specific massage techniques to the participant's neck area (as described above). Often times, this component is delivered while participants are in the prone position whereas "Specific Neck Work I" is delivered while participants are in the supine position.
Integration II	2-5	As described above and with the intention to begin the closure process of the treatment. Participant may be asked during this time if there are any additional areas that feel unfinished or would like more work—no new specific work is introduced during this time.
Completion	1-2	This component allows the massage therapist to provide a general closure to the treatment. Often times, clinicians have signature ways in which they may conclude treatment sessions using techniques that include gentle rocking, scalp work, finger-tip brushing, gentle compression, or soft verbal cues. Closure or completion time will often provide a general "signal" to the massage recipient that the session is concluding and allows the end to be expected and not abrupt. The intention here is to support participant relaxation and to provide transition to the posttreatment "world."

Massage Therapists

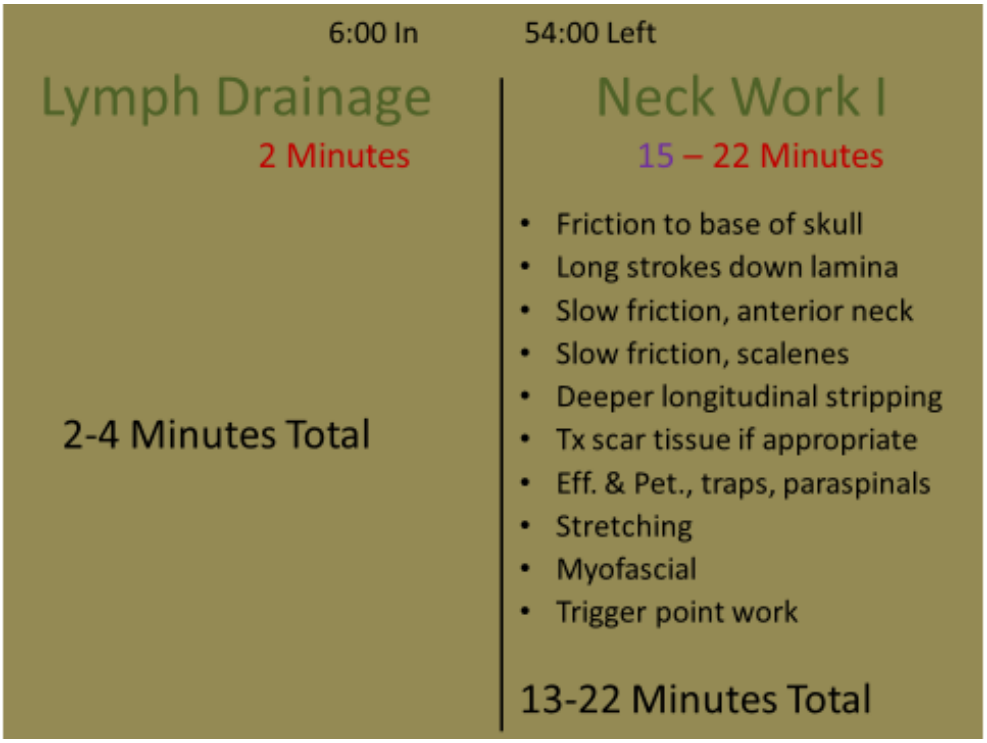
A total of 9 Indiana state–licensed massage therapists with a range of 3-25 years of experience (median 6 years) were recruited to deliver the massage protocol to participants randomized to the TT-M arm. Therapists were solicited to participate through general and word-of-mouth advertisement approaches and querying professional message organizations.

Study therapists required two types of training: (1) specific study protocols and procedures and (2) VA-required training for privacy and information security.

The study-specific training for protocol and procedures was conducted in person and lasted approximately 3.5 hours. The training was divided into general environment orientation, research processes including duties and responsibilities, and learning specifics related to delivering the massage protocol.

The massage therapist protocol adherence and fidelity were addressed in 2 specific ways. First, the therapists launched a timed and silent PowerPoint slide show on a treatment room computer positioned for easy viewing by the therapist during the session. The slide show was timed to advance every 30 seconds through the duration of the 60-minute session and displayed how much time had passed in the protocol, how much time was left in the protocol, the treatment component or components that could occur at that time, and the potential most (in red) and least (in purple) time available to complete any of the possible components (Figure 2). For applicable components, a list of possible techniques and approaches that could be performed during the component was listed as a reminder; therapists were not required to do all or any of the items listed. A silent 15- and 5-second warning (not shown in Figure 2) appeared at the bottom right of the component section to prompt therapist preparation for progress to the next component if needed.

Figure 2. Sample slide from therapist-delivered massage protocol adherence and fidelity PowerPoint. Eff: effleurage; Pet: petrissage; traps: trapezius (upper, middle, lower) Tx: treatment.



Second, massage therapists completed an electronic fidelity checklist after every session to further support intervention adherence and fidelity. The checklist consisted of 7 sections to ensure that each aspect of the treatment protocol was consistently completed: pretreatment protocol, treatment application protocol, and supported additional notes and documentation. The pretreatment protocol section asked therapists to verify the treatment date, if the participant attended, and that the hands-on, prespecific work aspects of the treatment were completed. The treatment application fidelity section asked therapists to indicate that each treatment protocol component was completed and any specific deviations that occurred. Finally, a note and checklist of allowable general techniques were available at the end of each fidelity checklist to indicate any additional notations.

WL-C Intervention

Participants in the WL-C arm received check-in calls at months 2 and 4 from the study staff and were administered outcome assessments on the same schedule (baseline and 1, 3, and 6 months) as the treatment groups. Participants in the WL-C were instructed to continue their medical care as normal and to not begin any massage treatment during the 6 months of the study.

Statistical Considerations

Sample Size Justification

The primary contrasts of interest were between the treatment arms (TT-M and CA-M) and WL-C, although analysis of all pairwise comparisons was planned. On the basis of the results from Sherman dosing study [29,31], the change in Neck

Disability Index (NDI) at 3 months in the TT-M arm is expected to be significantly better than that in the WL-C arm (effect size=0.8 SD). Greater improvement in the CA-M arm over the WL-C was also expected, assuming a medium effect size (0.5 SD). The initial sample size was determined using a 2-sample independent 2-tailed *t* test. With 396 patients (132 per treatment group), TOMCATT would have 80% power to detect a medium effect size (0.4 SD) among treatment groups in the NDI at the 3-month time point with type I error set at 0.017 (0.05/3) to maintain familywise error at 0.05. An approximate 15% dropout rate at 3 months was expected, and it was initially planned to enroll 468 patients (156 per treatment group).

Statistical Analysis

Overview

Balanced baseline characteristics of the study participants is expected across the 3 treatment groups due to randomization. Baseline demographic and clinical characteristics will be compared among the treatment groups using the appropriate tests. Variables found to be significantly different will be included in the subsequent regression models.

Main Analysis (Aim 1) of the Primary Outcome (NDI Total Score)

All outcomes are collected at baseline and 1, 3, and 6 months. For the primary outcome of the NDI total score, a linear mixed effect model will be used with an appropriate covariance structure to compare each treatment arm to the WL-C arm on change scores at the 3-month time point. Fixed effects will include treatment, time (as categorical), and treatment by time interaction. Differences in change scores among groups at other time points (1 and 6 months) will also be reported. Associations among repeated measures within participants will be examined, and a data-driven approach will be used to determine the appropriate variance-covariance structure [32]. The Šídák method will be used to adjust for multiple comparisons. Type I error will be set at 0.017 for the primary comparisons to maintain the familywise error at 0.05. An intent-to-treat approach is planned with the primary end point at 3 months and evaluation of "early" response at 1 month and "sustained" response at 6 months after randomization.

Analysis of Secondary Outcomes (Aim 2)

TOMCATT is not specifically powered for secondary outcomes, and a cautious interpretation of the secondary analysis results is planned. For pain intensity, those with a clinically relevant >30% reduction from baseline will be reported as "responders." For the NDI, a "responder" will be defined as a decrease of >5 points from baseline to 1, 3, and 6 months for each participant. A generalized linear mixed model with predictors of group, time, and their interaction will be used. The model will also include a random subject effect to accommodate the potential correlation among observations from the same participant [33]. The primary contrast of interest will be the difference in proportions at 3 months between each treatment and the WL-C group. Similar regression modeling strategies will be used to assess the exploratory outcomes of pain coping, sleep problems, satisfaction, and social support.

Moderator Analyses

Baseline anxiety (General Anxiety Disorder-7) and depression (Patient Health Questionnaire-9) will be tested as potential moderators of the primary outcome (NDI), as well as secondary outcomes, as secondary analysis. Testing these measures as moderators will provide insight into the generalizability of the interventions. For example, if the intervention loses effect in patients with high anxiety or depression, they may not be suited to the intervention.

Missing Data

Missing data in 2 different forms are expected: missing data by attrition and intermittent missing of observations. Attrition of <15% was expected at the 3-month follow-up. Differential attrition among study arms was expected during study planning or initiation, yet the potential that care ally burden could lead to more attrition in the CA-M arm and transportation barriers could lead to more attrition in the TT-M arm was acknowledged by the study team. The effects of missing observations due to attrition will be examined by analyzing the patient characteristics associated with dropout. Multiple imputation techniques may be used to alleviate the impact of missing data. However, if the pattern of missing data is nonignorable, more complex modeling approaches to model the missing data may be used. Finally, sensitivity analyses will be conducted to ensure the validity of study findings.

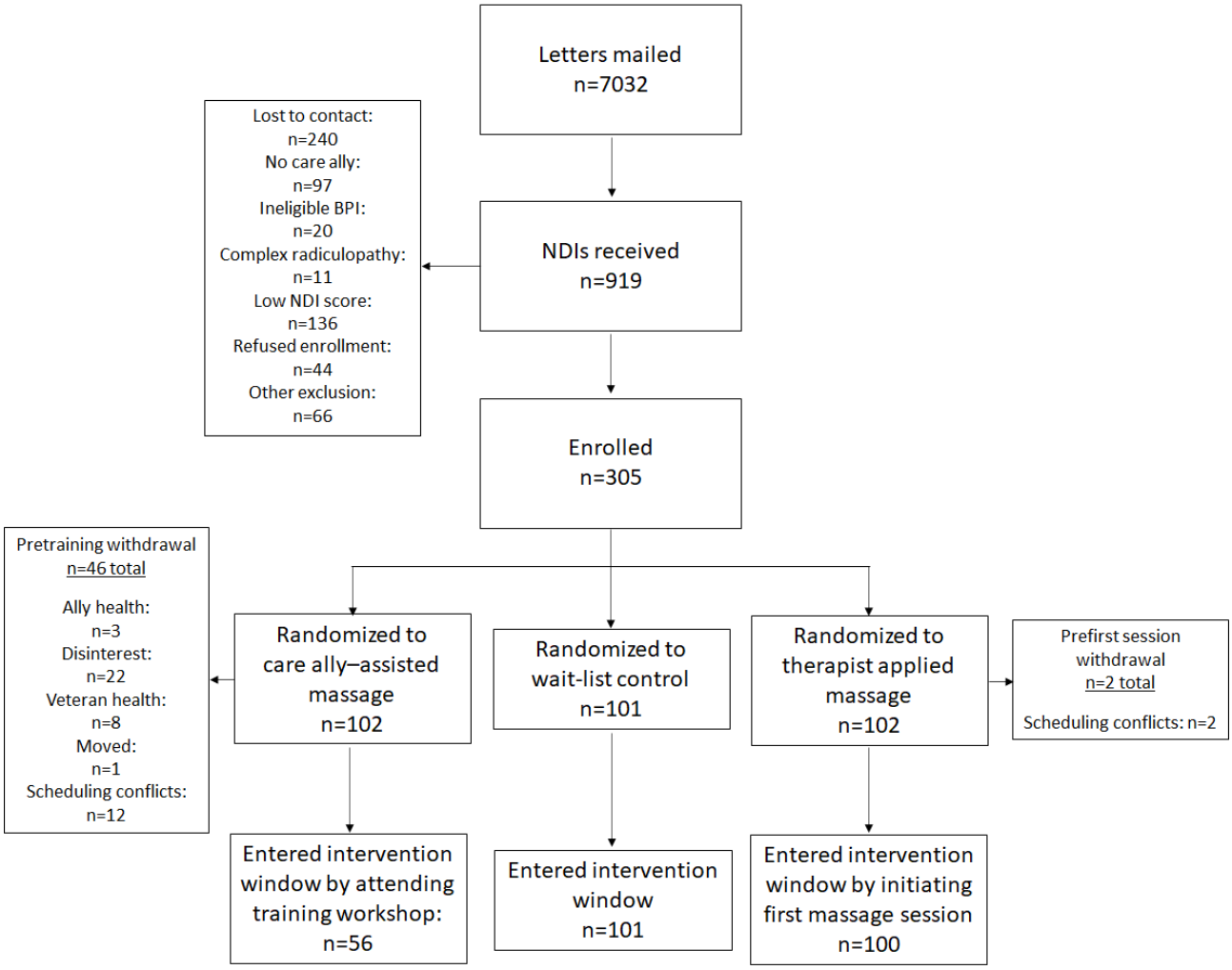
Results

Overview

The TOMCATT pretrial activities were launched in July 2016 and included massage therapist recruitment, training, and onboarding; the finalization of training materials; data collection documents and databases created; and research personnel hired and trained.

Participant recruitment began in May 2017. Figure 3 depicts the results of screening, eligibility determination, enrollment, randomization, and treatment initiation for the first 30 months of TOMCATT. Potential participants were identified through the electronic medical record as having CNP, of whom 7032 were sent a study invitation letter that included a screening NDI form for interested individuals to return to learn more and be further screened for enrollment eligibility. Various additional recruitment methods have been used, but their yield is unclear. The NDI screening forms yielded 33.2% (305/919) of the enrolled participants. In all, 14.8% (136/919) of the received NDI form scores did not meet the neck pain with disability thresholds required to participate, whereas another 26.1% (240/919) of potentially eligible participants returned NDI forms but could not be contacted.

Figure 3. Premodification recruitment, randomization, and intervention initiation flow diagram. BPI: Brief Pain Inventory; NDI: Neck Disability Index.



Participant Recruitment, Enrollment, Intervention Initiation, and Retention

Randomization resulted in 102, 102, and 101 participants in the CA-M, TT-M, and WL-C arms, respectively, in the first 30 months. All WL-C participants progressed to the 12-week nonintervention phase of the study, with 93.1% (94/101) completing an outcome assessment (data not shown). In all, 98% (100/102) of participants in the TT-M initiated the intervention. Of the 102 participants, only 2 (2%) failed to schedule and attend their first TT-M treatment and withdrew from the study owing to schedule conflicts.

For CA-M, only 54.9% (56/102) of the randomized patients attended training and initiated treatment. Disinterest was the primary reason (22/46, 48%) indicated for noninitiation, followed by scheduling issues (12/46, 26%). Among those who attended training, an average of 42 days passed between baseline data collection and training or treatment initiation. Participant engagement was further challenged by inconsistent treatment log-return compliance, despite most participants (52/56, 93%) completing one or more follow-up outcome assessments (data not shown). Nearly 45% (25/56) of participant dyads returned no compliance logs, whereas nearly one-third of the participants (17/56) returned logs for each of the 12 intervention weeks. A majority of CA-M dyads (31/56, 55%) returned at least one week of compliance logs.

Efforts to Improve CA-M Arm Treatment Initiation

Several mitigatory steps were taken to improve treatment initiation in the CA-M arm over approximately 14 months. To accommodate individual schedules, training workshops were scheduled 3 times per month, which included at least one Saturday, a morning training session during the week, and an afternoon training session during the week per month; any of which was held for as long as at least one dyad attended. Several additional training workshops were scheduled per individual dyad scheduling needs.

In an effort to retain participants in the CA-M arm and facilitate treatment initiation for those with care ally barriers, a matching approach was launched whereby former Veteran participants who expressed willingness were matched with enrollees who ultimately did not have a care ally willing or able to attend training and provide care ally–assisted intervention for 12 weeks. An enrollee with care ally participation barriers agreed to be matched but did not attend the scheduled training, despite the matched, stand-in care ally attending.

Although not initiated, a modified training approach was developed for CA-M arm participants as an alternative to the 3.5-hour training seminar. The modified approach was composed

of a combination of at-home learning and supportive applied laboratory experiences. The developed approach included participants accessing digitally recorded didactic information and materials from a supportive DVD on their own time in a structured and prompted format. Once complete, the dyad would schedule a 1-hour hands-on application session with NM to reinforce content and ensure safe and appropriate application of the intervention techniques.

Modified Trial Protocol

Overview

The decision to modify the TOMCATT design was informed by disproportionate attrition before treatment initiation and poor adherence to CA-M treatment logs. These challenges persisted, despite several procedural modifications to support participation and adherence. The modified study design to remove the CA-M arm was developed and approved by the study funder and institutional review board in November 2019 and December 2019, respectively. Participants enrolled and randomized to the study before the postmodification date progressed through study completion based on their original group assignment.

Modified Eligibility Criteria, Recruitment, Enrollment, and Randomization

The inclusion criterion for participants to have an identified care ally was removed from the modified study design. The recruitment and enrollment procedures remained the same. After modification to a 2-arm study, a new set of randomization lists was created. Within each strata defined by sex, patients were randomized 1:1 to the TT-M or WL-C group using block sizes of 4.

Modified Design Sample Size Justification

Because of high attrition in CA-M (62/98, 63%), TOMCATT was modified into a 2-arm study (TT-M and WL-C). The modified study will focus on comparison of the TT-M and WL-C. At modification, it was assessed that 100 patients per group (N=200) would provide 80% power to detect a 0.4 SD in NDI change from baseline between TT-M and WL-C with type I error of 0.05. The premodification attrition rate at 3 months in the TT-M and WL-C groups was 23.9% (47/197). Thus, the enrollment of 264 (200/0.76) or 132 per group was planned during the postmodification period. The comparison of CA-M to WL-C obtained before the study modification will be considered a secondary analysis and reported in a subsequent manuscript.

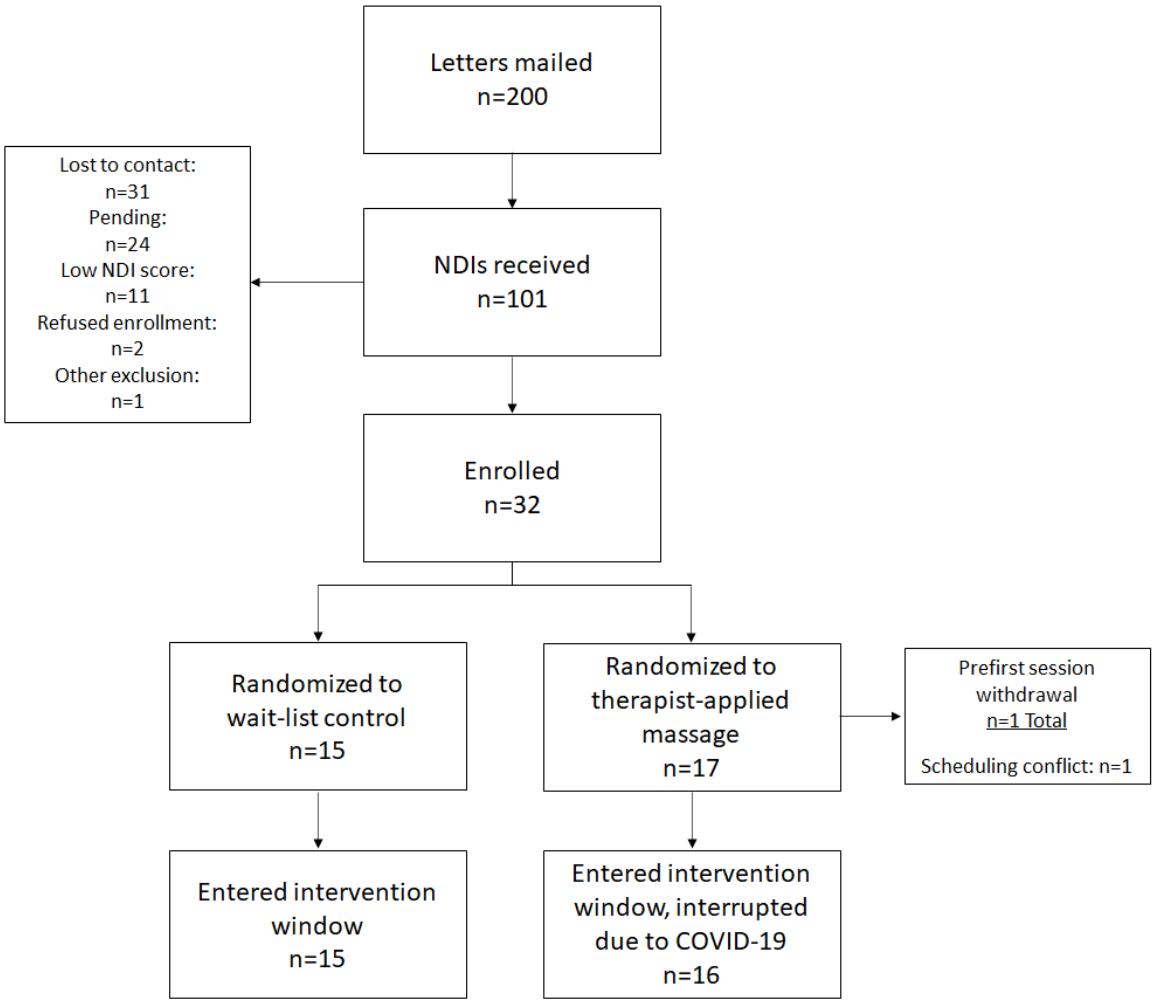
Modified Design Statistical Analysis

The analysis plan for the modified study will be conducted in a manner similar to that of the initial 3-arm randomized controlled trial. Randomization is expected to achieve balanced baseline characteristics of study participants among the study groups. Primary (NDI) and continuous secondary outcomes (pain intensity, depression, anxiety, and pain cognition) will be assessed using a linear mixed model approach. Type I error will be set at 0.05. The Šídák method will be used to adjust for multiple comparisons at a given time point for the secondary outcomes. Noncontinuous outcomes will be assessed using a generalized linear mixed model. In the revised design, missing data from attrition and intermittent missing observations are expected. Attrition of approximately 24% is expected by the 3-month follow-up and has been accounted for in the modified sample size calculation. The effects of missing observations due to sample attrition will be examined based on the patient characteristics associated with early dropout.

Modified TOMCATT Design Progress Through the Initiation of the COVID-19 Pause

Figure 4 displays the flow diagram for recruitment, enrollment, and treatment initiation from November 2019 to March 2020, when the COVID-19 pause began. Recruitment efforts resulted in 50% of the recalculated needed enrollment achieved in just over 4 months. Of those enrolled, all but one TT-M participant initiated treatment (TT-M).

Figure 4. Postmodification recruitment, randomization, and intervention initiation flow diagram. NDI: Neck Disability Index.



Discussion

Principal Findings

The TOMCATT trial was initially designed to test the effectiveness of 2 different massage interventions versus WL-C. Treatment engagement and retention challenges have emerged and raised questions about the feasibility of CA-M. Consequently, the study design was modified, resulting in a simpler, 2-arm study. This decision, although difficult, allowed the TOMCATT study team to focus and redirect recruitment efforts on the 2 remaining study arms. Promising recruitment and retention success for the postmodification efforts point to promising expectations for TOMCATT's resumption efforts from the COVID-19 pause.

Comparison With Prior Work

Caregiver-delivered massage has been shown to be feasible and effective in 2 previous Veteran-focused studies [10,11], but such an approach has not been studied for a chronic musculoskeletal pain population. The treatment engagement and retention challenges that disproportionately affected the CA-M arm were greater than expected, based on previously published studies [10,11]. It is speculated that these challenges have emerged for several reasons. First, participants randomized to the CA-M group may have been disappointed that they were not randomized to the TT-M group given the popularity of massage. It is well known that participants have strong preferences for treatment allocation within trials [34], and these preferences can impact follow-up rates, attrition, and treatment outcomes [35]. Second, dyadic research poses unique challenges in recruitment, retention, attrition, data collection, and analysis [36] relative to nondyadic research. Studies of chronic pain may heighten the challenges of dyadic research, because chronic pain can have a significant impact on a person's social relationships by triggering symptoms of anxiety, depression, and anger [37]. Third, CA-M was an intensive intervention that involved attending a one-time, multihour workshop; a DVD for regular home use; a treatment session log to complete weekly; and delivery of 30-minute massage sessions by the care ally 3 times a week for 12 weeks. The substantial time investment and significant requirement for active dyadic participation may have been too great for some participants who never engaged in the intervention or withdrew from the study.

The qualitative interview data collected in a subset of TOMCATT participants are anticipated to elucidate some challenges that emerged within the original design and may provide potential insights into ways to improve treatment engagement, retention, and interpret eventual trial results. In these interviews, the participants are asked about their prerandomization arm preferences, treatment perceptions, and

outcome expectations. Qualitative data collection and analysis may highlight a desire to incorporate treatment preferences into the design of future massage trials. Furthermore, assessing the sociodemographic and clinical correlates of treatment engagement and retention, especially among CA-M participants, are planned.

Limitations

This manuscript reports only preliminary findings related to enrollment and intervention uptake to explain the modification rationale from a 3-arm to a 2-arm study design and to describe the modification methodology. Furthermore, the COVID-19 pandemic has caused significant disruptions to TOMCATT, especially the delivery of TT-M. All in-person noncritical research activities were suspended in March 2020. Thus, all in-person TOMCATT activities, including delivery of massages, were forced to halt owing to safety concerns and institutional mandates. Because of intermittent surges in COVID-19 infection rates throughout 2020 and early 2021, TOMCATT continued to suspend in-person research activities owing to safety concerns for participants, massage therapists, and study staff. As a result, recruitment and massage treatment delivery for TOMCATT did not restart until June 2021, after infection rates had declined and safety mitigation factors were in place and believed to be effective. Study recruitment and enrollment began gradually with study capacity reached and a smooth process implemented by December 2021.

Conclusions

Although the use of informal caregivers to provide massage is an innovative care delivery model, it was not feasible in our study of Veterans with CNP, which was hampered by low engagement and high attrition. TOMCATT's continued efforts with the modified study design will provide a better understanding of the feasibility and effectiveness of an on-site therapist-applied massage treatment model for Veterans with CNP, an approach that demonstrates feasibility and acceptability. The incorporation of patient preferences into the study design is planned for future trials to improve engagement and retention in all care approaches.

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Data Availability

The data set supporting this article is not available. According to Department of Veterans Affairs policy, these data are stored behind the Veterans Affairs firewall and cannot be shared even after deidentification. Investigators interested in analyses of the existing data are encouraged to contact the corresponding author.

Authors' Contributions

All the authors contributed to the development of this manuscript. NM contributed to study design, data collection, interpretation, and writing. JKD contributed to statistical analysis and writing. EE contributed to study design, data collection, review, and editing. MK contributed to the study design, data collection, review, and editing. JES contributed to statistical analysis and writing. BL contributed to instrumental study support, data collection, and review. TF contributed to instrumental study support, data collection, and review. MSM contributed to study design and interpretation of results. MJB was the principal investigator and contributed to study design, results interpretation, and writing.

Conflicts of Interest

None declared.

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Abbreviations

CA-M: care ally–assisted massage
CNP: chronic neck pain
NDI: Neck Disability Index
TOMCATT: Trial Outcomes for Massage: Care Ally–Assisted Versus Therapist-Treated
TT-M: therapist-treated massage
VA: Veterans Affairs
WL-C: wait-list control group

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Protocol

A Care Concept of Community Health Nursing Interventions for Adults With Chronic Health Conditions in an Urban Area: Protocol for a Randomized Controlled Field Trial (CoSta Study)

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Abstract

Background: Implementing community health nursing programs is a new field of application in the primary health sector of Germany. Hence, there is limited evidence of effective community-based and nurse-led interventions with regard to the German health care system. International research findings are mostly not transferable. The Community Health Nursing in der Stadt (CoSta; ie, "Community Health Nursing in the City") project is the first study that examines a community health nurse–led intervention for adults with chronic health conditions.

Objective: This study protocol describes the design and methods of a randomized controlled field trial that will investigate if a community health nurse–based intervention has an impact on health-related quality of life in adults with chronic conditions.

Methods: The study was designed as a randomized controlled trial that will be conducted under real-life conditions in the field. In a 4-month period, patients with at least 1 chronic *International Classification of Diseases, Tenth Revision*, diagnosis will be enrolled. Participants will be randomly allocated to an intervention group or a control group. The sample size was assumed based on an effect size of 0.50 with a significance level of .05, using a 2-sided (2-tailed), 2-sample unequal variance *t* test. The control group will be treated as usual. The intervention group will receive—in addition to the usual treatment—preventive home visits; consultations; and educative training, which will be offered by 2 community health nurses for up to 12 months. Both groups will be followed up at baseline, after 6 months, and after 12 months. The primary outcome measure is the mental component summary score from the 36-Item Short Form Health Survey after 12-months. Secondary patient outcomes will be included. The study received ethics approval from the Competence Health Center's institutional review board at the University of Applied Sciences Hamburg (procedure number: 2020-14).

Results: The CoSta project was funded by the Federal Ministry of Education and Research Germany (contract number: 13FH019SX8). In total, 187 participants were recruited at the beginning of August 2021. Further, 92 were excluded and 94 were randomized. Data collection will be conducted until the end of 2022.

Conclusions: Our study will provide data with regard to the effectiveness of community nurse–led interventions that focus on the treatment of vulnerable adults with chronic health conditions in a community health center. In secondary analyses, the associations among influencing social factors (education, income, and employment) will be examined. We expect results that will help reduce the research-to-practice gap.

Trial Registration: German Clinical Trials Register DRKS00026164; https://tinyurl.com/yckxc5ut

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KEYWORDS

community health nursing; chronic health conditions; randomized controlled trial; community-based program; health-related quality of life; nurse-led consultation; nursing; nurse; intervention; urban; protocol; Germany; adults

Introduction

Background

The implementation of advanced nursing professionals in primary care has become a topic of public debate in Germany lately. The COVID-19 pandemic has emphasized already existing gaps and health inequalities in primary care and community settings. During the last 2 years, different studies reported a disproportionate impact on disease burden and well-being in vulnerable target groups, as well as socioeconomic disparities resulting from the pandemic event [1,2]. Neighborhoods with high rates of poverty, precarious employment, and discrimination are more affected by COVID-19 itself and the economic, psychological, and social consequences resulting from the pandemic [3]. Additionally, for people with (multiple) chronic health conditions, a higher risk of experiencing these effects, as a result of the pandemic event, has been reported [4]. Regional data on reported COVID-19 cases in Germany show increased mortality rates in socially disadvantaged districts [5], references to COVID-19–related outcomes (eg, infection rates), and correlations with social indicators [6]. The latest evidence does not differ from those reported in previous pandemics [7], revealing existing health-related inequity in societies [8] and underlining the important roles of community and public health services and authorities. In Germany, this evidence has intensified the discourse on gaps in the health care system. It is not news that primary care is under threat, particularly as there is a lack of health services in certain rural and urban districts that exacerbates unequal access, especially among socially disadvantaged populations [9]. Moreover, it is well known that there is a gap in life expectancy (up to 10 years between high-income and low-income individuals) in Germany. These differences also exist for the majority of people with chronic health conditions. Such health inequalities are largely the result of social determinants of health [10]. Therefore, using nurse-centered approaches in the community could be a sustainable solution. According to successfully implemented international role models, the community health nursing (CHN) concept [11] has been discussed for the primary health sector in Germany [12,13]. Nurse professionals at the master's degree level provide evidence-based care and health promotion in various settings (eg, in community health centers [CHCs]), addressing vulnerable groups and their particular needs [14]. The initiative of the Robert Bosch Foundation (with the Agnes Karll Society and the German Professional Association of Nursing) to establish CHN and test master's degree programs in Germany [13], as well as a recently published legal requirement [15], has advanced this ongoing debate. In other countries, such as Canada, this nurse profile has been implemented in health services for several years [16]. However, international research findings are mostly not directly transferable to the German health care system. The legal framework for CHN's scope of action is still lacking [13], and funding for CHN and CHN's anchoring in the laws on benefits must be reviewed [13]. Accordingly, CHN still needs to be developed in Germany, and more information and evidence are needed about the effectiveness of community-based nurse interventions and their impact on socially determined health inequalities. The CHN in der Stadt (CoSta; ie, "Community Health Nursing in the City") project is the first project that evaluates CHN interventions for patients with chronic health conditions who live in a disadvantaged neighborhood (Hamburg-Veddel). The social disadvantages that many residents experience in this neighborhood manifest as high unemployment rates, low household incomes, and a high dependence on state transfer payments, when compared to other districts of the city [17]. Furthermore, health challenges are reflected in the neighborhood by both the higher prevalence of chronic conditions, such as hypertonus, and the low utilization of outpatient care [18].

The CoSta project was funded in 2020 by the German Federal Ministry of Education and Research. For the project, a community nurse–led care concept targeting chronic conditions has been developed. The research questions of the CoSta study aim at exploring how community health nurse interventions impact health-related quality of life, health literacy, coping, depressive symptoms, anxiety, social participation, and the utilization of health services among patients with chronic health conditions. Furthermore, we assume that social disadvantage will correlate with the impact on chronic health conditions and the use of health care services. In the secondary analyses, we will focus on the effects of education, employment, and income on health. To answer the research questions, a randomized controlled trial (RCT) will be conducted for 1 year. The CoSta project is being realized via a joint effort by the University of Applied Sciences Hamburg and Community Health Centre Policlinic Veddel. Statistical advice has been provided by the Institute of Medical Biometry and Epidemiology at the Medical Center Hamburg-Eppendorf. The purpose of this study protocol is to describe the RCT, which was designed to examine the effectiveness of a new community health nurse concept among adults with chronic health conditions. This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

Objectives

The aim of the CoSta study is to explore the effects of a new nurse health care concept on patients with chronic health conditions (ie, effects on primary and secondary outcome measures) and compare them to the effects of usual treatment. The primary alternative hypothesis is that participants in the intervention group will experience greater improvements in the mental components of their health-related quality of life compared to those experienced by participants in the control

group over a 12-month period. The following research questions will be addressed in secondary analyses:

- How do the outcomes of patients regarding health-related quality of life, depressive symptoms, anxiety, health literacy, coping, social participation, and the utilization of health care differ between groups (nurse-led intervention group and usual care group)?
- How should nurse-led consultations be designed?
- How can nurse-led health promotion interventions be implemented in the neighborhood?

Methods

Trial Design

The CoSta study was designed as a prospective, monocentric, 2-armed RCT that will evaluate the effectiveness of community nurse–led interventions for adults with chronic conditions from an urban area in Germany. A 1:1 allocation ratio for the intended number of participants in each of the two groups will be used. The primary and secondary outcomes that will be assessed in the study are guided by the principle that defines *health* as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity," as stated in the Constitution of the World Health Organization [19]. The methodological procedure is based on the methods of a Canadian study that evaluated an interprofessional, nurse-led program for promoting self-management in older adults with multiple chronic conditions [20]. A participant timeline recommended by the SPIRIT guidelines was generated to visualize the planned process of enrollment, interventions, and selected validated assessment instruments (Multimedia Appendix 1).

Study Setting

The study will enroll adult patients with chronic health conditions who are treated in a CHC and will involve a multiprofessional team of general practitioners, clinical psychologists, social workers, midwives, and advanced nurses who provide health care in the community. The clinic is located in the Hamburg-Veddel district, which can be described as a socially disadvantaged urban neighborhood wherein about 5000 people live in a densely built housing estate surrounded by railroad tracks, highways, and a port and industrial area. The residents are comparatively young, and many are dependent on state transfer payments [17]. Chronic health conditions, such as diabetes mellitus, hypertension, heart failure, and lung diseases, are highly prevalent [18]. Further, the amount of primary care offerings are comparatively below the average. Interprofessional cooperation will play a great part in developing the program. The two interventionists have their own office, and both participate in interprofessional case conferences and supervision meetings.

Eligibility Criteria

The criteria that were chosen will allow for the broad inclusion of current patients with chronic diagnoses from the CHC. Participants who fulfill the following criteria will be enrolled: (1) patients who provide informed consent, (2) patients aged ≥18 years (no limit), (3) patients who are registered as patients at the CHC, (4) patients with a diagnosis of at least 1 chronic condition, and (5) patients who live at home.

Patients who do not fit the criteria for the study, refuse to participate, or are experiencing a severe course of disease will be excluded. Furthermore, people living with dementia or an acute psychiatric diagnosis and patients living in foster care will be excluded from enrollment.

Interventions

The framework of the CHN concept is based on the "critical-emancipatory concept of nursing action" [21]. The CoSta program is a 12-month, patient-driven, multicomponent intervention that was developed to empower patients with chronic health conditions in managing their illness. It consists of the following three different types of nurse-led interventions: (1) home visits offered once per month by the community health nurse, (2) weekly consultations offered by the community health nurse, and (3) monthly training sessions that are tailored to the course of a chronic disease and are hosted by specialist practitioners or the interventionists themselves. During the home visits and consultations, assessments, physical examinations, and care coordination and planning will be carried out by the community health nurse. During the weekly consultations, assessments, care coordination and care navigation (linking participants to other health care services) will be conducted by the community health nurse. During 4 additional topic-centered consultation hours (each will occur once per month), which will be dedicated to cardiovascular diseases, lung diseases, chronic pain, and diabetes mellitus, as well as specific disease counseling, will be offered. Professional translators will be brought in for the interventions, as needed.

Patients who are randomly assigned to the intervention group will be offered all of the aforementioned interventions in addition to the usual treatment that they receive in the CHC. The interventionists will not deliver any health services to participants who are randomly assigned to the control group. These participants will be offered treatment as usual. Because the CHN concept involves patient-tailored interventions, the content of the interventions will differ among participants to some degree due to individual patient needs and the course of the health condition.

Outcomes

The surveys will take place at baseline (t_0), after 6 months (t_1), and after 12 months (t_2). The primary patient-reported outcome of the study is the mental dimension of the health-related quality of life items (mental component summary [MCS] score; 12 items) from the 36-Item Short Form Health Survey (SF-36), which will be measured as changes in MCS scores from t_0 to t_2. We will use the self-report SF-36 questionnaire, which includes retrospective questions about the previous 4-week period. The SF-36 includes 36 questions regarding subjective health status. It has been psychometrically tested and normed for Germany [22,23]. For secondary patient-reported outcomes, the following instruments will be used: (1) the physical dimension of the health-related quality of life items (physical component summary score; 12 items) from the SF-36 [22,23]; (2) the summary score of depression scale from the Patient

Health Questionnaire-9 [24]; (3) the short form of the German version of the European Health Literacy Survey Questionnaire (HLS-EU-Q47; HLS-EU-Q16-GER [includes 16 items from the HLS-EU-Q47]) [25]; and 6 scales from the HLS-EU-Q47 [26], Index for the Assessment of Health Impairments [27], and Essen Coping Questionnaire [28].

Participant Timeline

Multimedia Appendix 1 shows the timeline of study phases, as recommended by the SPIRIT guidelines, for the enrollment, intervention, and assessment time points.

Sample Size

A power analysis was done a priori. The sample size was calculated with the Power Analysis & Sample Size 16.0.3 program (NCSS LLC) to demonstrate group differences in the primary outcome (MCS scores). The assumptions were based on a study by Markle-Reid et al [20]. The sample size was estimated based on an effect size of 0.50 with a significance level (α) of .05, using a 2-sided (2-tailed), 2-sample unequal variance *t* test (experimental group sample size: mean 55.3, SD 7.8; control group sample size: 53.5, SD 9.6). The maximum number of cases was limited to 130 in order to guarantee that the interventions will be offered to every participant in the intervention group during the limited study period. This maximum sample size of 130 (65 per group), which was calculated based on the aforementioned input parameters, yields 64.1% power to reject the null hypothesis.

Recruitment

Recruitment was conducted for 5 months, from August (the first patient was recruited on August 10, 2021) to the end of December 2021, in cooperation with the multiprofessional team (physicians, physician assistants, clinical psychologists, social workers, and midwives) at the CHC. The eligibility of participants was determined by the CHC staff, who were trained in advance. Based on the inclusion criteria, the staff identified patients with at least 1 chronic diagnosis and then contacted them directly. A recruitment protocol was used. Patients received a letter of information that included notes on the study aims, study design, data protection, and randomization. The information was available in 6 languages—Turkish, Macedonian, Albanian, English, French, and German. Participation is voluntary, and consent can be withdrawn at any time without incurring disadvantages in treatment. In addition, once per week, a nurse (and a bachelor of arts student) supported the recruitment process at the CHC in order to clarify questions. After verbal consent was obtained, patients were contacted by a research assistant by telephone for further information. Questionnaires were designed as self-report surveys and were administered after a 48-hour consideration period and the provision of written consent. If there is a need for assistance, home interviews or interviews at the CHC will be offered by study assistants.

Assignment of Interventions (for Controlled Trials)

Sequence Generation

After the baseline survey, a statistician from the Institute of Medical Biometry and Epidemiology at the Medical Center Hamburg-Eppendorf randomly assigned included study participants to the intervention group or control group (stratified by gender). Randomization was realized via a computer-based permuted block design with variable block lengths to generate the allocation sequence, in which the number of assignments to the intervention group satisfied the 1:1 allocation ratio. The allocation concealment mechanism is described in the next subsection.

Data Collection, Management, and Analysis

After randomization, the interventionists were informed about the group assignments because they are the ones who will implement the interventions. This was also necessary for informing the participants about the allocations. The research assistant who is responsible for data extraction and analyses was blinded and excluded from the entire recruitment process.

Data Collection Methods

Data will be collected primarily at baseline (t_0), after 6 months (t_1), and after 12 months (t_2). At baseline, data will be collected on the primary and secondary outcomes (described in the *Outcomes* section), in addition to variables on diseases, demographics, socioeconomic factors, the utilization of health services, and digital mobile health apps. The flow of participants through the study phases has been presented in a flow diagram that conforms to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [29] for pragmatic trial reporting (Multimedia Appendix 2).

Data Management

Surveys will be realized as paper and pencil assessments. For data input, descriptive statistics and statistical analyses, which will be conducted with SPSS Statistics version 22 (IBM Corporation), will be used. The double entry of data (primary data) has been planned for the first 10 questionnaires, and random checks will be performed as data entry progresses to check for input errors. Collected data from the baseline and follow-up assessments will be checked for missing data, plausibility, and outliers.

Statistical Analysis

For analyses, data from the intention-to-treat population will be used. Data from the baseline survey will be analyzed descriptively to compare the demographic, socioeconomic, and clinical characteristics of study participants. Means and SDs or medians and IQRs will be calculated for continuous variables, and absolute frequencies and proportions will be calculated for categorical variables. For the primary analysis, a mixed linear regression model will be used, with groups, time points, and gender included as fixed effects; participants included as random effects; and baseline values included as covariates. For the primary analysis, the treatment effect at t_2 will be evaluated, and the 2-sided significance level (α) will be set to 5%. To summarize the characteristics and outcomes of each group, as well as for the comparison of the groups, descriptive statistics and appropriate tests will be used. For regression models, gender will be included as a fixed effect, as per the stratification used in the randomization process. Other covariates (eg, age and the number and duration of diagnoses of chronic illness) will be

included in sensitivity analyses. Following the study analysis procedures of Markle-Reid et al [20], the correlation between the quantity of utilized interventions and the primary outcome will be analyzed.

Ethics Approval

Ethics approval was obtained from the institutional Competence Health Center's ethics commission at the University of Applied Sciences Hamburg in March 2021 (procedure number: 2020-14). The study will be conducted in accordance with the commission's ethical standards and the Helsinki Declaration.

Results

The RCT was developed to evaluate a community health nurse model for primary care settings. Funding for conducting the CoSta study was provided by the Federal Ministry of Education and Research Germany in 2020 (contract number: 13FH019SX8). In total, 187 participants were recruited at the beginning of August 2021. Further, 92 were excluded and 94 were randomized. Surveys will be conducted until the end of 2022. A summary of the results will be published in peer-reviewed journals and presented at scientific conferences after the completion of the t_2 surveys (ie, by the end of 2022).

Discussion

Study Overview

The CoSta study will evaluate a community health nurse–led intervention for enhancing the well-being of patients with chronic health conditions in an urban neighborhood. By using a randomized trial design, the feasibility and benefits of the CoSta intervention will be compared to those of usual treatment. Thus, the study will focus on advanced nursing practitioners' role in Germany and will offer an approach to targeting the needs-oriented care of patients with chronic illnesses.

Via a randomized group comparison, the analyses will generate data on health-related quality of life, depressive symptoms, anxiety, health literacy, coping, and the utilization of health care in the study population. Furthermore, influencing social aspects and local contexts will be taken into consideration.

The study results could contribute to informing stakeholders in the health care system about responsibilities that can be applied universally in primary care. The expected results could reduce the research-to-practice gap, and they could serve as a basis for the transfer the care model to other regions and the German health care system.

Strengths and Limitations

A strength of the CoSta study and the nurse-led model is the integration of a multiprofessional team within the CHC. Additionally, the study design can be applied directly in the field. The study will be conducted with the cooperation of the study participants. The CoSta study will provide evidence-based information about a new approach in health care for providing a better quality of life to patients with (multiple) chronical illnesses in a more socially disadvantaged neighborhood. The study results can be used to support other ongoing projects [13,14] that target the anchoring of CHN in Germany.

Due to the field conditions however, there are limitations that can be expected throughout the study period. First, there will probably be a greater need for trained staff during the entire study period. Particularly for the recruitment and education of study participants before study enrollment, the study nurse was a supportive team member for recognizing barriers at an early stage. Second, due to the global COVID-19 pandemic, it was difficult to identify and recruit patients with chronic illnesses. As such, a longer period for recruitment would have been useful.

Harms

The participants are a vulnerable group due to their chronic health conditions. As experienced nurses, the researchers involved will be able to engage appropriately with the patients, manage spontaneous adverse events, and terminate participation (if necessary). For participants, there will be opportunities to ask questions before and during the data collection process and trial interventions.

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Data Availability

The data sets that will be generated during the study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Schematic diagram of the Community Health Nursing in der Stadt study phases, as recommended by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.
[PNG File , 65 KB - resprot_v11i9e37965_app1.png]

Multimedia Appendix 2
Flow diagram of progress from enrollment to analysis (CONSORT [Consolidated Standards of Reporting Trials] 2010 flow diagram).
[PNG File , 168 KB - resprot_v11i9e37965_app2.png]

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Abbreviations

CHC: community health center
CHN: community health nursing
CONSORT: Consolidated Standards of Reporting Trials
CoSta: Community Health Nursing in der Stadt
HLS-EU-Q16-GER: short form of the German version of the European Health Literacy Survey Questionnaire
HLS-EU-Q47: European Health Literacy Survey Questionnaire
MCS: mental component summary
RCT: randomized controlled trial
SF-36: 36-Item Short Form Health Survey
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Melatonin for Neuropathic Pain: Protocol for a Double-blind, Randomized Controlled Trial

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Abstract

Background: Neuropathic pain (NP), a complication of several conditions (eg, diabetic neuropathy and varicella zoster), is a common challenging problem, and there is a growing need to develop safe and effective nonopioid treatments. Sleep disturbance is commonly associated with NP because pain intensity in NP conditions is often worse at night. The pineal hormone melatonin has been shown to reduce pain in both preclinical and clinical settings, in addition to multiple trials demonstrating efficacy for primary insomnia and delayed sleep phase syndrome.

Objective: We propose to conduct a clinical trial to evaluate the efficacy and safety of melatonin for NP.

Methods: Using a double-blind, placebo-controlled, crossover design, 30 adults with NP will be randomly allocated to one of two sequences of treatment with melatonin and placebo. During each of the two treatment periods, participants will take capsules containing melatonin or placebo for 4 weeks, followed by a 7-day washout period. The primary outcome will be mean daily pain intensity (scored 0-10) at maximally tolerated doses (MTDs) during each period. Secondary outcomes, assessed at MTDs, will include global improvement, adverse events, mood, and quality of life.

Results: This trial was registered in the International Standard Randomized Controlled Trial registry May 4, 2022 (ISRCTN #16215617), attained conditional ethics approval May 9, 2022 (Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board protocol number ANAE-387-22), and recruitment is set to start August 2022.

Conclusions: This trial will provide rigorous evidence comparing the efficacy of melatonin to that of placebo in the treatment of NP.

Trial Registration: ISRCTN Registry 16215617; https://www.isrctn.com/ISRCTN16215617

International Registered Report Identifier (IRRID): PRR1-10.2196/40025

(JMIR Res Protoc 2022;11(9):e40025) doi:10.2196/40025

KEYWORDS

melatonin; neuropathic pain; chronic pain; sleep; analgesic therapy; placebo; clinical trials; neuropathic; pain; nonopioid; treatment; efficacy; insomnia; placebo; preclinical; clinical

Introduction

Neuropathic pain (NP) is a common form of secondary chronic pain due to a lesion or disease of the nervous system [1] such as diabetic neuropathy, spinal radiculopathy, HIV-neuropathy, postherpetic neuralgia, and cancer-related conditions [2]. NP has been estimated to have a prevalence of 7%-8% [3] and is known to impair physical, social, and occupational function with a subsequent devastating impact on patients, their families, and society [4,5]. Oral medications may be a valuable element of multimodal NP management owing to their ease of administration and engagement of drug effect sites throughout the sensory nervous system [6,7]. However, studied treatments provide only partial benefit owing to incomplete efficacy and dose-limiting adverse effects (AEs) [8].

Chronic pain, including NP conditions, is commonly associated with sleep disturbance. Complex interactions between pain and sleep are such that effective therapy requires coordinated attention to the interaction between pain and sleep [9,10]. In patients with chronic pain, observations suggest that a night of poorer sleep is followed by a more painful day, and a more painful day is followed by a night of poorer sleep [11]. Thus, in addition to treating one of the most prominent secondary features of chronic pain, pain therapies that also improve sleep may be expected to have more favorable efficacy [12].

Melatonin (N-acetyl-5-methoxytryptamine), a hormone secreted by the pineal gland, has been implicated in several homeostatic functions including sleep, modulation of circadian rhythms and mood, enhanced immunity, and antioxidant free radical scavenging [13]. Relevant to pain, accumulating preclinical and clinical evidence suggests antinociceptive effects of melatonin by acting on MT_1 and MT_2 membrane receptors (to reduce cyclic AMP) but possibly also (1) by indirectly activating opioid receptors, (2) by inhibiting the production of proinflammatory cytokines, (3) by activating γ-aminobutyric acid-A receptors, and (4) through its antioxidant effects [14]. Emerging evidence suggests that melatonin reduces pain in both preclinical and clinical (fibromyalgia) settings [15-17], in addition to multiple randomized controlled trials (RCTs) demonstrating efficacy for primary insomnia and delayed sleep phase syndrome [18]. After oral administration, melatonin undergoes first-pass hepatic metabolism [19], with subsequent secondary renal metabolism and elimination [20]. A review of studies involving varying doses [21] reported that oral administration of melatonin results in a transport maximum ranging 15-210 minutes, and a half-life ranging 28-126 minutes [21].

Thus, in the interest of further evaluating the analgesic efficacy of melatonin for NP, our objective is to conduct a double-blind RCT to compare the efficacy of melatonin to that of placebo in patients with chronic neuropathic conditions.

Methods

Ethics Approval

This study has been submitted to, and is currently under review by, the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (protocol #ANAE-387-22). This study protocol will be conducted in accordance with the principles of the Declaration of Helsinki, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' guidelines [22,23], and in accordance with the International Council for Harmonisation Good Clinical Practice: Consolidated guideline. This trial has been funded by the Physicians' Services Incorporated Foundation and was registered in the International Standard Randomized Controlled Trial Registry on May 4, 2022 (ISRCTN #16215617).

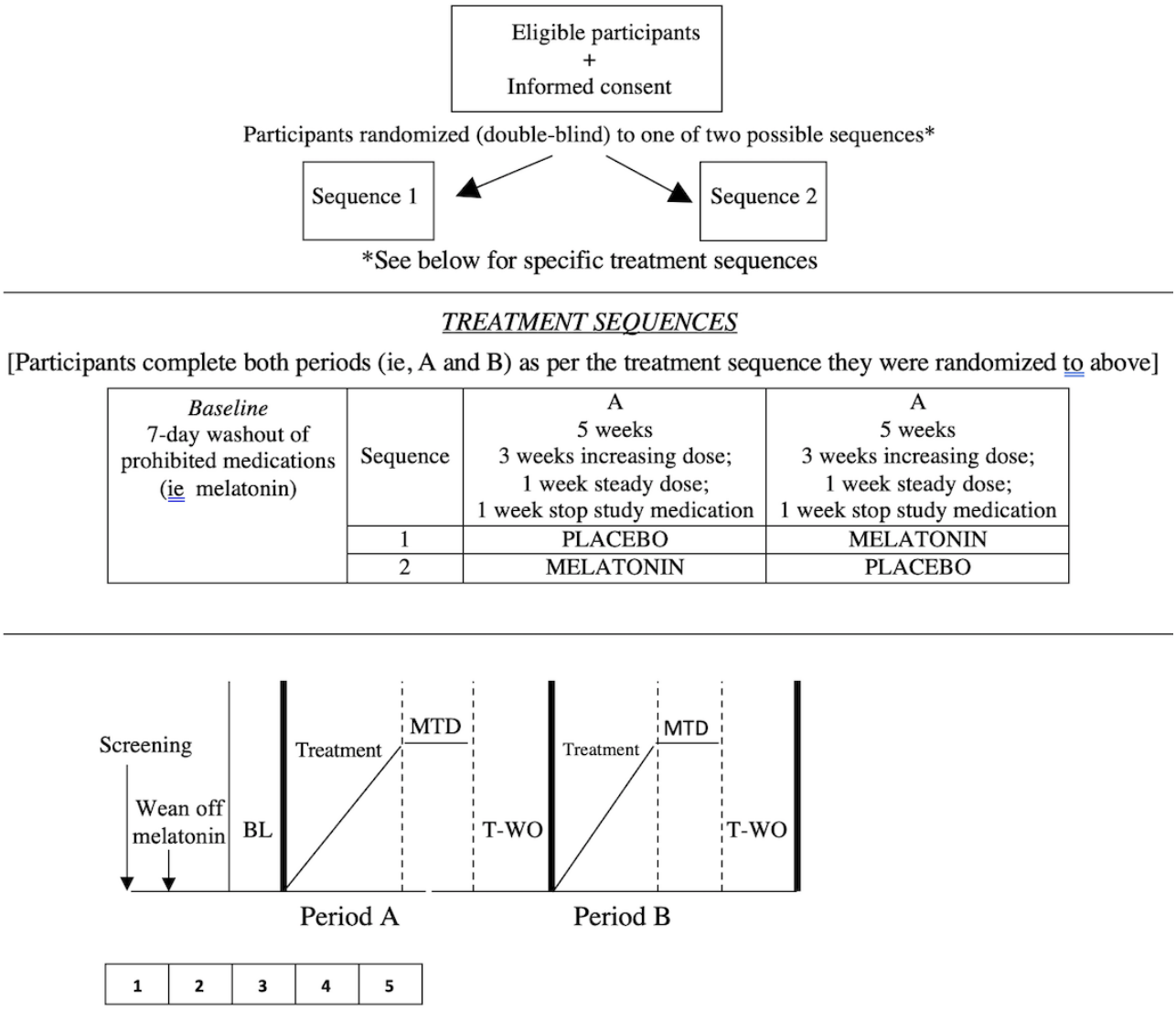
Aims and Hypothesis

The objective of this trial is to evaluate the efficacy, safety, and tolerability of melatonin in treating pain in participants with chronic neuropathic conditions. Our primary hypothesis is that melatonin is safer than and superior to placebo and is well tolerated in treating neuropathic pain.

Design

This is a double-blind, randomized, controlled, 2-period, crossover trial comparing melatonin to placebo in adults with chronic neuropathic pain (Figure 1). Both treatment periods will be 5 weeks in duration, and the entire trial will be 10 weeks long for each participant. Participants will be randomized to one of the two treatment sequences. The randomization sequence will be generated using the web-based program randomization.com (Dallal, Tufts University). Participants in sequence 1 will take active melatonin capsules during the first 4 weeks of the trial (followed by a 1-week washout period) and will subsequently take inert placebo capsules for the next 4 weeks of the trial (followed by a 1-week washout period). Participants in sequence 2 will take inert placebo capsules during the first 4 weeks of the trial (followed by a 1-week washout period) and will subsequently take active melatonin capsules for the next 4 weeks of the trial (followed by a 1-week washout period). Figure 1 shows a schematic representation of the trial design.

Figure 1. Clinical Trial Schema.



Setting

Investigators work at a tertiary care health sciences center (Providence Care Hospital) in Kingston, Ontario, Canada.

Participants

Men and women meeting the diagnostic criteria for peripheral NP will be considered for recruitment following informed consent. The inclusion criteria are as follows: (1) a score of 4 or higher on the DN4 interview—a validated questionnaire that distinguishes between neuropathic and nonneuropathic pain [24]; as indicated, investigations will be performed to confirm an NP diagnosis including, but not limited to, nerve conduction studies and electromyography; (2) daily pain (score of ≥4/10) for at least 3 months; (3) alanine transaminase level≤120% of the upper normal limit; (4) creatinine clearance of ≥60 mL/min; (5) glycosylated hemoglobin of ≤9.5%; and (6) necessary abilities, visual acuity, and language skills for questionnaire completion and telephone communication with nurses. The exclusion criteria are as follows: (1) major organ system disease; (2) cardiovascular autonomic neuropathy; (3) trigeminal neuralgia, complex regional pain syndrome, or central NP; (4) moderate to severe sedation or ataxia due to other required concomitant drugs; (5) allergy or hypersensitivity to study medications or any components in the study drug formulations or its containers; (6) seizure disorder; (7) other painful conditions that are >50% as severe as their NP; (8) a major, poorly controlled psychiatric disorder, depression or suicidal ideation, or active substance use disorder; (9) candidates who live alone and cannot assure daily contact with a friend, family member, or caregiver; (10) women of childbearing potential who will not receive a highly effective form of contraception (total abstinence, hormonal birth control methods, intrauterine devices, confirmed successful vasectomy of the partner, double barrier methods such as condom or diaphragm, etc) or a positive pregnancy test at baseline (If a study participant becomes pregnant, she must stop using study medications immediately and will be withdrawn from the study); (11) women who are breastfeeding or who plan to breastfeed; (12) regular daily administration of opioids at a dose greater than 90 mg morphine equivalents; and (13) lack of a primary care physician.

Randomization and Blinding

We will use a balanced Latin Square crossover design [25-27] in which participants will be allocated to one of the two treatment sequences: melatonin and placebo. At the beginning of the trial, an investigational pharmacist will use a computer-generated randomization process to prepare a concealed allocation schedule to randomly assign the treatment sequences in appropriate block sizes to a consecutive series of numbers. On enrollment, each participant will be assigned to the next consecutive number, and the corresponding series of study medications will be dispensed (eg, melatonin followed by placebo or placebo followed by melatonin). Study medications will be formulated in an identical fashion across treatment periods. Treatment codes for each study participant will be generated by an investigational pharmacist and will not be disclosed to study personnel or participants until completion of the trial. Study outcome measures will be evaluated and recorded by the research study nurse who will be blinded (as will the rest of the research team) to treatment group assignments until trial completion. As an assessment of blinding to the treatment group, each participant and the study nurse will complete a blinding questionnaire at the end of each treatment period.

Cointerventions and Rescue Medication

Any enrolled participants already taking melatonin will be weaned off during a pretrial washout of at least 7 days. Participants taking and perceiving benefit from opioids (<90 mg morphine equivalents), antidepressants (tricyclic, selective serotonin reuptake inhibitor, or serotonin-norepinephrine reuptake inhibitor), nonsteroidal anti-inflammatory drugs, or acetaminophen may continue these medications at a steady daily dose for the duration of the study. Any ongoing cognitive behavioral therapy or exercise programs perceived as beneficial will be allowed to continue only if it is certain that these will be evenly used throughout the trial. Participants will not be allowed to start new medications, cognitive-behavioral therapy, or exercise programs at any point during the study. Participants will be required to avoid any procedural pain therapies (eg, neurosurgical interventions, nerve blocks, or acupuncture) during the study. Participants will be permitted to take acetaminophen (≤8 tablets, 325 mg/tablet daily) for inadequate pain relief only during the taper and washout phases of each treatment period. Acetaminophen consumption will be recorded as a secondary outcome measure.

Study Treatment Dosing Schedule

During each period of this trial, participants will receive 1 set of capsules (melatonin capsules, Bio-tech Pharmacal) containing 3 mg melatonin or placebo (lactose capsules). Each period will last 5 weeks, with a 4-week treatment period and a 1-week washout period. During week 1 of each treatment period, participants will take 1 capsule before bedtime. During week 2, participants will take 2 capsules before bedtime. During week 3 participants will take 3 capsules before bedtime, and during week 4, participants will take 4 capsules before bedtime. The ceiling dose for melatonin is 12 mg/day. With each increase in the dosage of study medication in the titration schedule, if mild to moderate treatment-emergent AEs (eg, sedation) are encountered, participants will be asked if they can tolerate continuing at that dose for another 2-3 days. If so, this dosage will be continued with the expectation that tolerance to side effects will occur. If side effects are severe, intolerable, or do not improve, both study medications will be decreased to the next lowest possible dose and an increase will be attempted one more time at the next scheduled dose increase. If this again results in intolerable side effects, both study drugs will be decreased back to the previous dose, which will be defined as the maximal tolerated dose (MTD) for that individual. However, during this flexible dose titration, the final dose arrived at during the MTD week (week 4 of the treatment period) could be lower than the ceiling dose of 12 mg if side effects encountered during the dose titration (eg, excessive sedation) are suspected to be due to melatonin.

Outcome Measures

During the trial, the study nurse will contact participants by telephone at least once a week to evaluate adverse effects, assess pain intensity, and encourage compliance. Furthermore, participants will be evaluated at the clinic on 1 of the 5 weekdays of week 4 of each treatment period for vital signs and assessment of secondary outcomes. Finally, participants will be followed up by telephone 2 weeks and 3 months following the completion of the study to document any subsequent problems or adverse events. Table 1 shows the schedule of study assessments.

The primary outcome is the mean daily "average" pain intensity [28] experienced while on the MTD of melatonin or placebo during week 4 (days 22-28). This will be determined from participants' ratings of their "average pain over the last 24 hours" completed in patient diaries every morning using a numerical rating scale from 0 to 10. Given the potential circadian variability of pain intensity [29], clinical trial methods have involved the following: (1) requiring participants to rate their pain multiple times through the day or evening [26,27], which increases participant burden and may adversely affect participant retention or missing data or (2) requiring participants to provide a retrospective rating of their "average pain over the last 24 hours" [30], which may be susceptible to recency bias. Based on our experience, we are proposing the latter approach, although both approaches have led to valid and generalizable trial results in clinical pain trials. Secondary outcomes include frequency or severity of treatment-emergent AEs; scores on the Neuropathic Pain Symptom Inventory [31], Medical Outcomes Study Sleep Scale [32], Patient Global Impression of Change [33], Brief Pain Inventory [34], Beck Depression Inventory-II [35], Beck Anxiety Inventory [36], the short-form McGill Pain Questionnaire [37], the SF-36 survey [38], and blinding questionnaires; and acetaminophen consumption. All these outcomes will be assessed at baseline and during week 4 of each treatment period, except for AEs and acetaminophen consumption, which will be assessed weekly during each treatment period.

Table 1. Schedule of study assessments.

Assessments	Screen	Baseline	treatment periods			3-month posttrial completion
			First 3 weeks of treatment	Fourth week of treatment	Washout	
Days per treatment period >	–14	–7	1-21	22-28	29-35	
Present pain intensity (scale 0-10; average and worst)	✓					
Concurrent medications[a]	✓	✓	✓	✓	✓	✓
Demographics and medical history	✓					
Vital signs and weight	✓			✓		
Clinical laboratories	✓					
Adverse events[a]	✓	✓	✓	✓	✓	✓
Drug dispensing		✓		✓		
Drug compliance and accountability				✓		
Daily pain diaries		✓	✓	✓	✓	
Maximum tolerated dose levels			✓	✓	✓	
Medical Outcomes Study Sleep Scale		✓		✓		
Other adverse effects[a]			✓	✓	✓	
Patient global impression of change			✓	✓	✓	
Brief Pain Inventory		✓		✓		
Beck Depression Inventory–II	✓	✓		✓		
Medical Outcomes Study 36item shortform health survey		✓		✓		
Rescue acetaminophen[a]			✓	✓	✓	
Blinding questionnaire				✓		
Neuropathic Pain Symptom Inventory		✓		✓		
Pregnancy test for women of childbearing potential	✓					

[a]Evaluated during weekly participant telephone contacts with the research nurse.

Sample Size

Statistical considerations underlying this sample size calculation are based on the null hypothesis that there is no difference in pain intensity between the study treatments and the alternative hypothesis that melatonin is different from placebo. Systematic reviews of placebo-controlled chronic pain trials consistently reveal that significant differences between treatment and placebo groups vary between 0.5 and 1.5 points, depending on the magnitude of the placebo response in any given trial [22]. Thus, based on a previous estimated within-participant variation of 2.5 from studies on NP [26], we project that a sample size of 21 participants would allow for an 80% chance of detecting (α=.05) a mean treatment group difference of 1.5 points on a 0-10 numerical rating scale. In order to have a sample size divisible by 4, we have adjusted the sample size to 24 participants. Accounting for trial dropout rates from our previous trials and for a 2-period crossover design, we expect that the recruitment of 30 enrollees for each trial will yield the aforementioned number of completers.

Statistical Analysis

Participants who complete both treatment periods will be included in trial analyses. When data from only one period are available, sensitivity analysis including all participants will also be performed, by assuming some reasonable but extreme values for the remaining periods. Those receiving at least one dose of study drug will be included in the safety analyses. The primary outcome will be calculated as an average of pain scores as recorded in the participant pain diaries within the last 7 days (at MTD in week 4 of the treatment), if more than 50% of the information (at least 4 days) is not missing [39]. Otherwise, mean daily pain will be treated as missing data. Sensitivity analyses based on the average of all available pain scores will also be performed to confirm the results of the primary analysis. A linear mixed model with sequence, period, treatment, and the

first-order carryover effects as fixed effects and participant as a random effect [39] will be used to test whether there is any treatment difference among groups and to estimate the least squares mean of the mean daily pain intensity for each treatment group, adjusting the carryover and period effects. The comparison between melatonin and placebo will be performed on the basis of the least squares means and SDs from the linear mixed model. Sensitivity analyses will be performed using a pattern-mixture model [40] based on patterns of missing data to check the robustness of results in case data may not be missing at random.

Secondary outcomes will be analyzed similarly except that (1) only 1 measurement will be analyzed in the last week for the singular measures (ie, final week questionnaires), and (2) the scoring algorithms developed for the Brief Pain Inventory, the Beck Depression Inventory-II, the Beck Anxiety Inventory, and the SF-36 will be first used to derive the subscales or domains within these instruments, and the scores on these subscales or domains will be used as response variables in the linear mixed model analysis.

Results

This trial has been funded by the Physicians' Services Incorporated Foundation and was registered in the International Standard Randomized Controlled Trial registry on May 4, 2022 (ISRCTN #16215617), and conditional ethics approval was obtained on May 9, 2022 (Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board protocol number ANAE-387-22).

Discussion

NP remains a challenging condition to treat, with current recommended pharmacological therapies providing only partial relief from pain, sometimes exacerbating other symptoms [41]. To the best of our knowledge, this proposed RCT is the first to investigate the safety and efficacy of melatonin for the treatment of NP. Given the potential improvement of pain and sleep with melatonin, we expect to observe a significant difference between the melatonin and placebo groups with respect to the primary outcome of pain and the secondary outcome of sleep in patients with NP. Although there has been some previous interest in the use of melatonin for pain management, few trials have been conducted in clinical chronic pain, and most of these have involved participants with fibromyalgia [15-17] and only one trial involved participants with NP [42]. Therefore, we expect that this trial will provide much needed evidence to further guide the appropriate use of melatonin in the management of NP.

Potential threats to this trial include challenges with patient recruitment, early dropouts, noncompliance, and protocol violations. However, the planned study design as well as our experience with similar previous chronic pain trials will mitigate these threats. In particular, careful and frequent follow-up of trial participants, timely management of treatment-emergent AEs, and open communication between participants and trial personnel are, once again, expected to minimize trial dropouts and thus maximize participant retention. Furthermore, as with our past RCTs, noncompliance, protocol violations, and early dropouts will be minimized by our proposed crossover design, thorough study participant teaching, and close weekly follow-up of participants. Variations in melatonin bioavailability across trial participants may increase the overall variability in trial results; however, compared to a parallel-group trial, our proposed crossover design will reduce the impact of such variability, whereby each participant acts as their own control.

In light of the current lack of desperately needed new improved NP therapeutics, this trial is expected to provide evidence for a safer and more effective treatment for NP. The development of this proof-of-concept RCT of melatonin in NP will facilitate future confirmatory RCTs and the implementation of melatonin into practice.

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Data Availability

Study data are available from the corresponding author on reasonable request.

Conflicts of Interest

IG reports receiving personal fees from Adynxx, Biogen, Eupraxia, Novaremed, and Teva outside the submitted work. DEM reports receiving personal fees from Canopy Growth outside the submitted work. RM reports receiving consulting and speaking honoraria from AbbVie, Allergan, Eisai, Janssen, KYE Pharmaceuticals, Lallemand, Lundbeck, Neonmind, Otsuka, and Sunovion, and research grants from Canadian Biomarker Integration Network in Depression, Canadian Institutes of Health Research, Janssen, Lallemand, Lundbeck, Nubiyota, Ontario Brain Institute, and Ontario Mental Health Foundation. He owns shares of Neonmind Inc.

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Abbreviations

AE: adverse effect
MTD: maximally tolerated dose
NP: neuropathic pain
RCT: randomized controlled trial

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Protocol

Optimized Informed Consent for Psychotherapy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Informed consent is a legal and ethical prerequisite for psychotherapy. However, in clinical practice, consistent strategies to obtain informed consent are scarce. Inconsistencies exist regarding the overall validity of informed consent for psychotherapy as well as the disclosure of potential mechanisms and negative effects, the latter posing a moral dilemma between patient autonomy and nonmaleficence.

Objective: This protocol describes a randomized controlled web-based trial aiming to investigate the efficacy of a one-session optimized informed consent consultation.

Methods: The optimized informed consent consultation was developed to provide information on the setting, efficacy, mechanisms, and negative effects via expectation management and shared decision-making techniques. A total of 122 participants with an indication for psychotherapy will be recruited. Participants will take part in a baseline assessment, including a structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) disorders. Eligible participants will be randomly assigned either to a control group receiving an information brochure about psychotherapy as treatment as usual (n=61) or to an intervention group receiving treatment as usual and the optimized informed consent consultation (n=61). Potential treatment effects will be measured after the treatment via interview and patient self-report and at 2 weeks and 3 months follow-up via web-based questionnaires. Treatment expectation is the primary outcome. Secondary outcomes include the capacity to consent, decisional conflict, autonomous treatment motivation, adherence intention, and side-effect expectations.

Results: This trial received a positive ethics vote by the local ethics committee of the Center for Psychosocial Medicine, University-Medical Center Hamburg-Eppendorf, Hamburg, Germany on April 1, 2021, and was prospectively registered on June 17, 2021. The first participant was enrolled in the study on August 5, 2021. We expect to complete data collection in December 2022. After data analysis within the first quarter of 2023, the results will be submitted for publication in peer-reviewed journals in summer 2023.

Conclusions: If effective, the optimized informed consent consultation might not only constitute an innovative clinical tool to meet the ethical and legal obligations of informed consent but also strengthen the contributing factors of psychotherapy outcome, while minimizing nocebo effects and fostering shared decision-making.

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KEYWORDS

expectation management; psychiatry; risks and side effects of psychotherapy; risk; counseling; consent; shared decision-making; decision-making; ethics; nocebo effect; side effect; adverse effect; psychotherapy; mental health; nocebo

Introduction

Obtaining patients' informed consent represents a legal and ethical obligation for conducting psychotherapy, which is embedded in numerous codes of conduct of international psychological institutions (eg, American Psychological Association [1], European Federation of Psychologists' Associations [2]). Psychotherapists are legally bound to disclose information about the treatment, including all circumstances that might be essential for an autonomous decision (eg, § 630e, German Civil Code [3]). In an ethical framework, psychotherapists should strive to balance the 4 moral principles of respect for autonomy, beneficence, nonmaleficence, and justice [4]. The major components of a truthful informed consent are (1) the decision-making capacity of the patient, (2) disclosure of treatment information, (3) voluntariness, (4) patient understanding, and (5) the explicit statement of consent [4,5].

A key challenge in obtaining truthful informed consent is the required disclosure of the potential negative effects of psychotherapy. Balancing the principles of autonomy and nonmaleficence causes an ethical dilemma [6]. On the one hand, psychotherapists strive to provide transparent information about possible treatment risks to enable autonomous informed decision-making. On the other hand, the disclosure of risk information can be harmful in itself, as it might cause nocebo effects. The latter effects are usually described as adverse effects that are not caused by the procedure but by negative expectations or negative prior learning experiences [6,7]. Thus, patients who were initially informed about the potential side effects at the beginning of psychotherapy are suggested to be more likely to experience these disclosed side effects than patients who did not receive this information before.

In clinical practice, informed consent procedures often fall short of legal and ethical recommendations of truthful informed consent [8,9]. So far, informed consent does not seem to be an integral part of clinical routine [10,11]. Empirical research, however, provides evidence that patients experiencing mental disorders have extensive information and decision-making needs [12,13]. Thus, a one-size-fits-all approach for providing consent information that neglects individual information needs may be insufficient.

Recent research suggests that the informed consent procedure might be underestimated in its clinical relevance to strengthen the contributing factors of psychotherapy outcome [5]. There are already first indications that the disclosure of transparent and contextualized information can effectively optimize treatment expectations [14]. Since treatment expectations are considered a key mechanism of change in psychotherapy [15], it is conceivable that truthful informed consent might elicit relevant expectation effects that reinforce treatment outcome [5,16]. Moreover, the autonomous treatment motivation and treatment adherence of patients might be strengthened [17,18]. However, it remains unclear how these key predictors of psychotherapy outcome can be optimally addressed in a tangible informed consent procedure.

Framing, contextualization, and shared decision-making might represent 3 promising strategies to optimize informed consent procedures. First, positive information framing might contribute to overcoming the dilemma of presenting transparent information about risks of psychotherapy on the one hand and preventing nocebo effects on the other hand [19]. Empirical findings suggest that positive framing may reduce side-effect expectations [14] and nocebo side effects [20]. Second, contextualizing information might positively influence treatment expectations and reduce decisional conflicts [6,14]. Third, integrating shared decision-making strategies might promote patient-centered care [21,22]. Advanced approaches for addressing, integrating, and implementing those strategies within an elaborate informed consent procedure are still missing in clinical practice to this day [20,23].

In summary, 3 major research gaps can be identified. First, empirical data about whether and how psychotherapists obtain informed consent in clinical practice are sparse. In particular, the integration of risk information has not been investigated so far. Second, there is a lack of concrete implementation strategies for an informed consent procedure that simultaneously accounts for legal, ethical, and clinical functionalities. Third, the effects of informed consent procedures on factors contributing to psychotherapy outcomes have not yet been investigated systematically. The latter 2 research gaps will be specifically targeted in this study. An optimized informed consent consultation (OIC) for psychotherapy has been developed as a new clinical tool based on the most recent empirical evidence. OIC will be applied in a web-based context for 2 reasons: (1) to increase accessibility and (2) to reduce health risks due to the ongoing pandemic. As the web-based context requires access to the internet for all participants and the study staff, potential interferences due to internet connection problems will be considered by providing clear instructions to participants with backup weblinks and contact information via phone.

This study aims to investigate the efficacy of OIC for persons with an indication for psychotherapy. We hypothesize that treatment expectations, autonomous treatment motivation, and adherence intention increase to a greater extent in the OIC condition than in the treatment as usual (TAU) condition from baseline (T0) to the follow-up assessment (T2). Moreover, we assume that decisional conflicts and expectations about the side effects of psychotherapy decrease to a greater extent in the OIC condition than in the TAU condition from baseline (T0) to the follow-up assessment (T2).

Methods

Study Design

A randomized controlled superiority trial will be conducted in the web-based context. Participants with an indication for psychotherapy are equally assigned to one of the 2 trial conditions (either to OIC + TAU or to TAU alone). The trial includes 2 web-based study visits with an interval of 2 weeks between the visits and 2 follow-up assessments 2 weeks and 3 months later. Web-based study visits are conducted via RED connect, an internet platform providing video consultations compliant with the German Data Protection Directive. Written study information, informed consent, and questionnaire-based assessments are provided via the web-based software EFS Survey, which fulfills the international guidelines for information security (ISO 27001). This study has been designed in line with the Consolidated Standards of Reporting Trials (CONSORT) statement [24].

Participants

Recruitment

The target population for the trial are German adults with an indication for psychotherapy. Recruitment cooperation with the outpatient clinic of the Center for Psychosocial Medicine at the University Medical Center Hamburg-Eppendorf was instated. In addition, participants will be recruited through referrals from other cooperating outpatient facilities, physicians, psychotherapists, mailing lists, internet platforms, and social media.

Inclusion and Exclusion Criteria

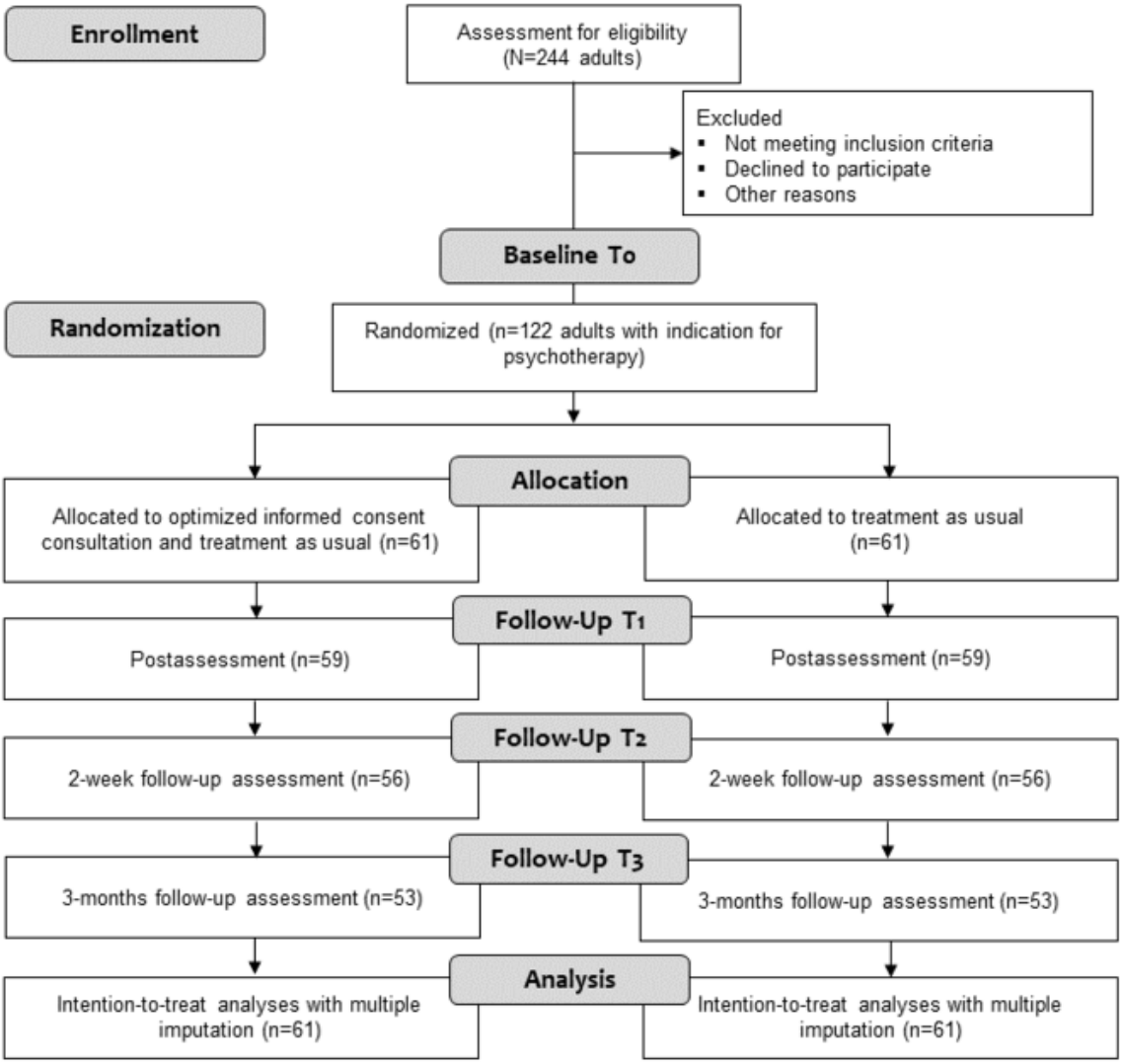
Participants need to (1) be older than 18 years of age, (2) have an indication for psychotherapy, (3) have an email account and a web-connected device with a camera and a microphone, and (4) provide informed consent for study participation and the use of an audio record. The indication for psychotherapy will be operationalized by at least one suspected diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) [25].

Exclusion criteria are (1) a current outpatient or inpatient psychotherapy, (2) utilization of probatory sessions for psychotherapy within the last 4 weeks, (3) insufficient language comprehension, (4) insufficient attention performance or cognitive capacity to participate in the interviews and OIC, and (5) acute suicidality. Exclusion criteria (3) and (4) will be evaluated by the study psychologist during the telephone screening and the clinical interview. Based on a criteria-led graduated scheme, acute suicidality will be evaluated by the study psychologist within the clinical interview. In case of acute crises, further predefined steps for action will be initiated.

Sample Size

The required sample size was a priori calculated using the G*Power software. Based on a previous experimental study analyzing the effects of framing and personalizing information about endocrine treatment on side-effect expectations in healthy women [14], a small-to-medium effect size can be expected for the impact of OIC on the primary outcome (treatment expectations). For two-tailed testing and a predetermined α level of .05, 106 participants would provide 80% power to detect significant interaction and the main effects of Cohen f=0.125 on the primary outcome. To compensate for an anticipated dropout rate of 15%, a total sample of 122 participants will be randomly assigned to one of the 2 groups (n=61 per group). Since it is assumed that at least 50% of all individuals can be included in the clinical trial after screening, approximately 244 individuals will need to be screened (see Figure 1).

Figure 1. Anticipated study flow chart.



Procedure

A telephone interview will take place before enrollment, in which oral study information will be given and interested persons are screened for self-reportable inclusion and exclusion criteria. If eligibility is given, interested persons will be invited for the first of the 2 web-based study visits that are conducted online by trained clinicians (Master of Science psychologists). At the first web-based study visit (T0), written information about the study will be given and the self-reportable inclusion and exclusion criteria will be queried. After providing their informed consent, participants will take part in a video-based Structured Clinical Interview for DSM-5 disorders (SCID-5) [26] to verify the indication for psychotherapy and check for exclusion criteria. If participants fulfill the eligibility criteria, the baseline assessment (T0) as well as the subsequent randomization will take place. At the end of T0, participants of both groups will receive TAU in form of an information brochure about psychotherapy. Participants will be invited to voluntarily study the brochure until the second web-based study visit (T1) 2 weeks later. At the second web-based study visit (T1), the intervention group will participate in the video-based OIC. Subsequently, all participants will take part in the postassessment and an interview for assessing the capacity to consent and adverse events. Upon request, participants will receive their individual results report of the SCID-5 within 1 week after T1. Two weeks (T2) and 3 months (T3) after T1, participants will be invited to complete 2 web-based follow-up questionnaires. A detailed summary of all the instruments is provided in Table 1.

Table 1. Schedule of enrollment, intervention, and assessment according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

	Study period					
	Screening	Enrollment	Intervention	Postallocation		
Time point	–1	T0		T1	T2	T3
Screening and enrollment						
Study information	✓	✓				
Eligibility screen	✓	✓				
Informed consent		✓				
Randomization		✓				
Intervention						
Treatment as usual + optimized informed consent consultation			✓			
Treatment as usual			✓			
Assessments						
Primary end point						
Treatment expectations (TEX-Q[a])		✓		✓	✓	✓
Secondary end points						
Capacity to consent (MacCat-T[b] interview)				✓		
Decisional conflict (DCS[c])		✓		✓	✓	
Side effects of psychotherapy: occurrence expectations, anxiety, and expected coping (3 constructed items)		✓		✓	✓	
Autonomous treatment motivation (ACMTQ[d] subscale)		✓		✓	✓	
Adherence intention (3 constructed items)		✓		✓	✓	
Interest in and knowledge about psychotherapy in general (2 constructed items)		✓		✓	✓	
Knowledge about what is meant by psychotherapy, its effectiveness, key mechanisms, side effects, legal and organizational aspects (5 constructed items)		✓		✓	✓	
Information-seeking behavior toward finding a treatment (3 constructed items)					✓	✓
Utilization of treatment services (6 constructed items)					✓	✓
Satisfaction with received information (CSQ-8[e])				✓		
(Expected) adverse events (interview)				✓	✓[f]	✓[f]
(Expected) serious adverse events (interview)				✓	✓[f]	✓[f]
Modulators						
Psychopathology (suspected diagnosis; SCID-5[g] interview)		✓				
State anxiety (STADI[h] subscale)				✓		
Prior knowledge about psychotherapy (FPTM[i] subscale)		✓				
Prior psychotherapeutic experience (G-EEE[j] subscale)		✓				
Satisfaction with therapeutic relationship (HAQ[k] subscale)		✓				
Time spent with the information brochure (single item)		✓		✓		
Sociodemographic characteristics (single item)		✓				
Intake of mental health medication (SCID-5 interview)		✓				

[a]TEX-Q: Treatment Expectation Questionnaire.

[b]MacCAT-T interview: MacArthur Competence Assessment Tool for Treatment.

[c]DCS: Decisional Conflict Scale.

[d]ACMTQ: Autonomous Motivation for Therapy Scale.

[e]CSQ-8: 8-item Client Satisfaction Questionnaire.

[f]At follow-up (T2 and T3), (serious) adverse events will be assessed by self-report instead of an interview.

[g]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-fifth edition.

[h]STADI: State Trait Anxiety Inventory.

[i]FPTM: Questionnaire on Psychotherapy Motivation.

[j]G-EEE: Generic Rating for Treatment Pre-Experiences, Treatment Expectations, and Treatment Effects.

[k]HAQ: Helping Alliance Questionnaire.

Study Intervention

OIC will be conducted online by trained study psychologists (Master of Science) at T1. For the purpose of conformity with a realistic preliminary psychotherapeutic consultation, OIC will last no longer than 35 minutes. OIC includes theory-overarching information about psychotherapy, clarifying what psychotherapy is, which forms and settings of psychotherapy exist, and how to get access to psychotherapy. The clinician will provide information about psychotherapeutic techniques, possible therapeutic objectives, the efficacy, and underlying mechanisms of psychotherapy. All 4 psychotherapeutic approaches that are recognized by the German social law (cognitive-behavioral psychotherapy, brief psychodynamic psychotherapy, psychoanalytic therapy, and systemic psychotherapy) are considered in OIC concerning their key mechanisms and techniques. In line with recent recommendations [23,27], OIC will contain information about the possible negative effects of psychotherapy (eg, the temporary increase of psychological strain) and respective individual coping strategies. Prior experience with psychotherapy and treatment expectations will be addressed since both are suggested to induce placebo and nocebo effects, which, in turn, might influence psychotherapy outcomes [7]. The clinician will target participants' expectations about outcome (ie, treatment benefit, positive and negative effects), process (ie, expected satisfaction, side effects, own impact, behavioral control), and their coping with potential side effects. In accordance with ethical demands [7,23], OIC will provide a realistic and nondeceptive yet positive description of psychotherapy.

During OIC, the strategies of framing, contextualization, and shared decision-making will be applied. Framing strategies as described by Barnes et al [20] will be applied by embedding information about the possible negative effects in information about the overall effectiveness of psychotherapy [7,28]. Information will be formulated gain-framed. Contextualization will be used to adapt evidence-based information about psychotherapy to the individual information needs as well as the psychological and living conditions of the participant [6]. In line with the shared decision-making approach, participants will be informed about treatment alternatives (eg, psychopharmacotherapy) and will be invited to express their views and preferences [29]. Participants will be actively involved in the discussion of options. A balanced relationship between the clinician and the participant will be supported by an empathic attitude of the clinician. As a multimodal presentation might increase the comprehension of information and is assumed to elicit larger framing effects on the reduction of nocebo side effects [20], information will be given orally with additional support of visual information cards.

TAU as a Comparator

To investigate the clinical significance of the newly developed OIC, a TAU condition will be used as a comparator. In both trial conditions, participants will receive an information brochure about psychotherapy from the Federal Chamber of Psychotherapists in Germany as TAU [30]. Participants may decide on their own whether and if so, how long they want to engage with the 80-page information brochure for psychotherapy patients.

Randomization

Stratified permuted block randomization with a block size of 4 permutations will be used to randomize participants 1:1 to the OIC and TAU conditions. Stratification will be based on prior experience with psychotherapy (no vs positive vs negative prior experience) to ensure that individuals with heterogeneous treatment experiences are balanced in both arms. Before the first enrollment, the randomization sequences will be generated by a researcher who is not involved in the study conduction by using a web-based program. At the end of the first web-based study visit, the responsible study psychologist initially determines the type of prior experience with psychotherapy by evaluating the information given by each participant. The randomizing officer will then conduct the allocation of each pseudonymized study case according to the randomization plan. Finally, the randomizing officer will inform the respective study psychologist about the group membership on a case-by-case basis.

Primary Outcome Measure

Participants' treatment expectation will be assessed using the Treatment Expectation Questionnaire [31]. The Treatment Expectation Questionnaire is a generic self-rating scale assessing patients' outcome and process expectations of medical and psychological treatments on 6 dimensions: treatment benefit, positive impact, adverse events, negative impact, process, and the behavioral control. The questionnaire consists of 15 items that are presented on an 11-point numeric rating scale. For all required analyses, mean subscale scores and the mean total score, each ranging from 0 to 10, will be used. Except for the subscales "adverse events" and "negative impact" with higher scores indicating lower treatment expectations, higher subscale

scores indicate higher treatment expectations. Treatment expectation as the primary outcome will be operationalized by the total mean score because it combines process and outcome expectations. To investigate the potential effects of OIC, the impact of OIC on treatment expectations will be additionally analyzed for each of the 6 subscales following an exploratory approach. To counteract the problem of multiple comparisons requiring multiple simultaneous statistical tests, statistical inference will be adjusted using the Bonferroni-Holm correction to reduce the risk of α error inflation.

Secondary Outcome Measures

The capacity to consent to treatment will be assessed by an adapted German version of the semistructured interview MacArthur Competence Assessment Tool for Treatment (MacCAT-T) [32,33]. Subscale scores, ranging from 0 to 6 (understanding), 0 to 8 (reasoning), 0 to 4 (appreciation), and 0 to 2 (choice), as well as the total sum score, ranging from 0 to 20, will be used for all required analyses. Higher scores indicate higher capacity to consent. Since the MacCAT-T provides a wide range of applications (eg, for dementia), the exact wordings of the questions have been rephrased and adapted to the psychotherapeutic context. Given that risks of psychotherapy may be diverse and multifaceted, it has been deemed sufficient if participants can name 1 risk of psychotherapy instead of 2, as demanded in the original form of the MacCAT-T. Thus, the maximum score of 2 in the item "understanding of benefits and risks" (subscale understanding) can be achieved, even if just 1 risk of psychotherapy can be expressed adequately. The ranges of all subscale scores as well as the range of the total sum score do not change due to this modification.

Decisional conflict will be assessed using the Decisional Conflict Scale [34,35]. The Decisional Conflict Scale consists of 16 items, which are divided into 5 distinct domains: uncertainty, informed, values clarity, support, and effective decision. All items are presented on a 5-point Likert scale, ranging from "not correct at all" to "fully correct." A total score and 5 subscale scores, each ranging from 0 to 100, will be used for analyses, with higher scores indicating higher decisional conflict. The perceived support in decision-making for or against the utilization of psychotherapy is assessed by 1 self-developed item that is presented on an 11-point Likert scale, ranging from 0 to 10, with higher scores indicating greater perceived support.

Three additional items were developed in advance to assess participants' (1) expectations about experiencing side effects of psychotherapy, (2) anxiety about experiencing side effects, and (3) expectations about coping with side effects. The corresponding items will be presented on an 11-point Likert scale, ranging from 0 to 10, with higher scores indicating higher expectation about occurring side effects, anxiety about side effects, or respective coping expectations.

The autonomous treatment motivation will be assessed by the translated subscale "autonomous motivation" of the Autonomous and Controlled Motivations for Treatment Questionnaire [36]. The translation from English to German was performed by a native English speaker. The subscale consists of 6 items, which are presented on a 7-point Likert scale, ranging from "strongly disagree" to "strongly agree." The subscale mean score ranges from 1 to 7, with higher scores indicating higher autonomous treatment motivation, and will be used for all required analyses.

The adherence intention for psychotherapy will be assessed by 3 self-developed items, which will be presented on an 11-point Likert scale, ranging from "not sure at all" to "absolutely sure." For all required analyses, the mean score will be used, ranging from 0 to 10, with higher scores indicating higher adherence intention.

Seven additional items were developed to assess (1) participants' interest in psychotherapy as well as their (2) knowledge about psychotherapy in general, (3) what is meant by psychotherapy, (4) the effectiveness of psychotherapy, (5) key mechanisms of psychotherapy, (6) side effects of psychotherapy, and (7) legal and organizational aspects of psychotherapy. The corresponding items will be presented on an 11-point Likert scale, ranging from 0 to 10, with higher scores indicating greater interest or higher knowledge.

The satisfaction with received information will be assessed by an adapted version of the German version of the Client Satisfaction Questionnaire [37,38]. The word "treatment" will be replaced by "received information" to increase the specificity. The 8 items will be presented on a 4-point Likert scale and summed up to a total score, ranging from 8 to 32, with higher scores indicating higher satisfaction with received information.

The information-seeking behavior toward finding a treatment will be assessed by 3 self-developed items, which will be presented on a 7-point Likert scale, ranging from "strongly disagree" to "strongly agree." The utilization of treatment services will be assessed by 6 self-developed items with the response options "yes" and "no."

As recently recommended by Papaioannou et al [39], (expected) adverse events and (expected) serious adverse events of OIC and of study participation per se will be assessed at postassessment by using a short interview. In addition to open questions about individual adverse events, 3 a priori developed items about potential adverse events (feeling confused, feeling frightened about potential negative effects of psychotherapy, experiencing doubts about the decision to start psychotherapy) and serious adverse events (suicidal ideation, self-harm, hospitalization) will be assessed. Each event will be rated by the interviewer according to severity (5-point Likert scale) and its potential causal relationship to the study participation (5-point Likert scale). For follow-up assessments (T2 and T3), a self-report will be used instead of an interview.

Blinding

Due to the nature of the study, neither participants nor the responsible study psychologists can be fully blinded toward the group membership. The assessment and analysis of the capacity to consent and the adverse events, however, will be carried out by researchers who are blinded regarding the randomization and do not otherwise interact with the respective participants throughout the entire course of the study. Questionnaire-based outcomes will be assessed pseudonymously via a web-based software, and the researcher conducting the statistical analyses will be blinded toward the randomized group allocation.

Bias Control

To reduce heterogeneity in content and risk of performance bias, OIC was manualized and all responsible study psychologists have been specifically trained by a licensed psychotherapist for conducting OIC. A licensed psychotherapist will supervise the study psychologists regarding the conducting of OIC throughout the study. To increase the interrater reliability and to reduce the risk of experimenter bias, all interviewers conducting the MacCAT-T interview have been trained and will be blinded to group allocation. Based on an audio record, an independent and blinded interviewer will conduct a second rating of the MacCAT-T.

Statistical Analyses

Linear mixed modeling for repeated measures will be conducted for the hypothesis referring to the primary outcome. Following the intention-to-treat approach, all randomized participants will be included in the analysis to avoid attrition bias. The model will contain one between-subject factor treatment (OIC + TAU vs TAU) and one within-subject factor time (T0, T1, and T2). Before linear mixed modeling, additional variables (eg, respective baseline scores, type of prior experiences with psychotherapy, prior knowledge about psychotherapy, satisfaction with the therapeutic relationship, state anxiety, the time of occupation with the information brochure) will be checked for significant associations with the respective outcomes to identify potential covariates. If there are additional covariates, they will be included in the linear mixed model. Group differences will be checked using Tukey posthoc tests. In case of imbalanced group sizes, Bonferroni-corrected posthoc tests will be carried out instead.

The analytical strategy of fitting linear mixed models will also be applied to all analyses, including secondary outcomes. Three exceptions for the described analytical strategy will be analyses including the secondary outcomes of capacity to consent, satisfaction with received information, and (serious) adverse events, for which group differences at postassessment will be examined by an independent sample two-sided *t* test, a Welch *t* test, or a Mann-Whitney *U* test. Intergroup differences at baseline will be detected using independent sample two-sided *t* tests, Welch *t* tests, or Mann-Whitney *U* tests (for continuous variables) and Pearson chi-square tests (for categorical variables). Partial eta squared will be reported for estimating the proportion of explained variance, with η^2=0.01 indicating small, η^2=0.06 indicating moderate, and η^2=0.14 indicating large effects [40]. Cohen *d* will be determined as a measure of effect size for pairwise comparisons (standardized mean differences) by dividing the mean score difference between the groups to be compared by the pooled standard deviation. According to Cohen [40], values of *d*=0.2, *d*=0.5, and *d*=0.8 are considered to indicate small, medium, and large effect sizes, respectively.

Missing values will be imputed using the multiple imputation technique but only if more than 2% of the data is missing. In case of multiple imputation, analyses will be repeated based on per-protocol analyses as a sensitivity analysis. If less than 2% of the data is missing, no multiple imputation will be carried out and a sensitivity analysis will be conducted using the last observation carried forward method. Each hypothesis will be tested two-sided with an α level of .05. All statistical analyses will be performed using SPSS version 27 (IBM Corp).

Ethics Approval

This trial is performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Center for Psychosocial Medicine, University-Medical Center Hamburg-Eppendorf, Hamburg, Germany (reference: LPEK-0292, 01.04.2021). The data generated from this study will be available for scientific purposes in PsychArchives (a disciplinary repository for psychological science) [41]. All participants provide informed written web-based consent for participation and for the publication of anonymized data for scientific purposes in the disciplinary repository.

Results

The first participant was enrolled on August 5, 2021. We expect to complete data collection in December 2022. After data analysis within the first quarter of 2023, the results will be submitted for publication in peer-reviewed journals in summer 2023. Research reports will be additionally disseminated through scientific forums, including presentations at conferences.

Discussion

The aim of this two-armed randomized controlled superiority trial is to evaluate the efficacy of a newly developed OIC for psychotherapy under consideration of its legal, ethical, and clinical functionalities. In this trial, the effects of an OIC combined with TAU is compared to those of TAU alone in a sample of German adults with an indication for psychotherapy. OIC was developed under consideration of the latest empirical evidence concerning the legal, ethical, and clinical requirements of a truthful informed consent procedure, including possible strategies to promote and integrate these functions. A semistructured guideline with supportive visual information cards was developed. Since OIC will take relatively little time and does not require advanced professional trainings, it might be a cost-effective tool for daily practice.

Noteworthily, a genuine clinical approach for integrating risk information into the informed consent for psychotherapy has been missing to this day. If proven effective, future patients might be adequately informed about possible risks of psychotherapy without violating the ethical principle of nonmaleficence. This multifaceted evaluation of a structured OIC might help reduce the initial reservations of psychotherapists about informing patients about the possible negative effects. Thus, OIC may represent the first feasible approach of fulfilling the legal demands of informed consent in clinical practice.

The web-based context was chosen to enable the participation of citizens living in rural areas with limited capacity of health care services. Since OIC is not restricted to a certain therapeutic approach, its scope of application is broad. In line with the current implications from psychotherapy research [42,43], OIC

might contribute to a theory-overarching dissemination of recent empirical evidence into the care system.

Nevertheless, this trial will have some limitations that need to be acknowledged. Although the web-based context should help expanding the spectrum of recruitment, it might also lead to the exclusion of potential participants who do not have a suitable internet connection. Moreover, no conclusions can be drawn regarding the specific efficacy of each of the 3 applied strategies, namely, contextualization, framing, and shared decision-making. However, if identified as efficient, the impact of each subcomponent of OIC may further be analyzed on a factorial basis.

To this day, efforts to implement risk information into informed consent for psychotherapy seem to be rather insufficient. The newly developed OIC for psychotherapy might contribute to bridging the gap between theoretically assumed ideals of truthful informed consent and practical realities.

Data Availability

Data sharing is not applicable to this paper as no new data were created or analyzed in this study. The data sets generated during this study will be available in anonymized form for scientific purposes in the publicly available PsychArchives (a disciplinary repository for psychological science) [41].

Authors' Contributions

LG, SL, and YN designed the study. LG and SL are carrying out the trial. YN, MT, and MH provide clinical supervision and assist in participant recruitment. LG drafted the manuscript. SL, FP, MT, MH, and YN commented and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders-fifth edition
MacCAT-T: MacArthur Competence Assessment Tool for Treatment
OIC: optimized informed consent consultation
SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-fifth edition
TAU: treatment as usual

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Protocol

An Evaluation of a Web-Based Decision Aid for Treatment Planning of Small Kidney Tumors: Pilot Randomized Controlled Trial

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Abstract

Background: Surgery is the most common treatment for localized small kidney masses (SKMs) up to 4 cm, despite a lack of evidence for improved overall survival. Nonsurgical management options are gaining recognition, as evidence supports the indolence of most SKMs. Decision aids (DAs) have been shown to improve patient comprehension of the trade-offs of treatment options and overall decision quality, and may improve consideration of all major options according to individual health priorities and preferences.

Objective: This pilot randomized controlled trial (RCT) primarily aims to evaluate the impact of a new web-based DA on treatment decisions for patients with SKM; that is, selection of surgical versus nonsurgical treatment options. Secondary objectives include an assessment of decision-making outcomes: decisional conflict, decision satisfaction, and an understanding of individual preferences for treatment that incorporate the trade-offs associated with surgical versus nonsurgical interventions.

Methods: Three phases comprise the construction and evaluation of a new web-based DA on SKM treatment. In phase 1, this DA was developed in print format through a multidisciplinary design committee incorporating patient focus groups. Phase 2 was an observational study on patient knowledge and decision-making measures after randomization to receive the printed DA or institutional educational materials, which identified further educational needs applied to a web-based DA. Phase 3 will preliminarily evaluate the web-based DA: in a pilot RCT, 50 adults diagnosed with SKMs will receive the web-based DA or an existing web-based institutional website at urology clinics at a large academic medical center. The web-based DA applies risk communication and information about diagnosis and treatment options, elicits preferences regarding treatment options, and provides a set of options to consider with their doctor based on a decision-analytic model of benefits/harm analysis that accounts for comorbidity, age group, and tumor features. Questionnaires and treatment decision data will be gathered before and after viewing the educational material.

Results: This phase will consist of a pilot RCT from August 2022 to January 2023 to establish feasibility and preliminarily evaluate decision outcomes. Previous study phases from 2018 to 2020 supported the feasibility of providing the printed DA in urology clinics before clinical consultation and demonstrated increased patient knowledge about the diagnosis and treatment options and greater likelihood of favoring nonsurgical treatment just before consultation. This study was funded by the National Cancer Institute. Recruitment will begin in August 2022.

Conclusions: A web-based DA has been designed to address educational needs for patients making treatment decisions for SKM, accounting for comorbidities and treatment-related benefits and risks. Outcomes from the pilot trial will evaluate the potential of a web-based DA in personalizing treatment decisions and in helping patients weigh attributes of surgical versus nonsurgical treatment options for their SKMs.

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International Registered Report Identifier (IRRID): PRR1-10.2196/41451

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KEYWORDS

small kidney mass; decision aid; renal tumor; randomized controlled trial; shared decision-making; decisional conflict

Introduction

Surgical resection remains the most common treatment for small kidney masses (SKMs; up to 4 cm in diameter, clinical stage T1a), though overall survival benefits have not been realized [1]. This troubling trend may be due to postsurgical worsening of kidney function and associated cardiovascular mortality in this generally older population with high rates of kidney disease, offsetting benefits of early tumor detection [2,3]. Although the majority of these SKMs are malignant, a small minority of tumors metastasize during a period of active surveillance, and approximately 20% are benign [1,4,5]. In fact, most kidney tumors are diagnosed as early-stage, incidental lesions on imaging tests performed for unrelated reasons [6,7].

Nonsurgical alternatives, such as percutaneous ablation and active surveillance with or without biopsy, may be considered to avoid surgeries in patients with indolent or benign tumors or in patients with risk factors for poor postsurgical outcomes. Therefore, we set out to determine the optimal management strategies for patients with SKMs and create evidence-based, patient-centered tools to communicate personalized harms and benefits of treatment options and promote shared decision-making. A decision-analytic model was developed to identify the key parameters, provide thresholds for variables affecting the decision (eg, test performance characteristics needed to improve outcomes), and assess the sensitivity of the decision to patient preferences [8]. We then interfaced the favored treatment options in accordance with patient and tumor characteristics with a decision aid (DA). DAs have shown benefit in these areas in treatment selection for prostate and breast cancer; while a DA has been published for kidney tumor management, consideration of specific features that can affect outcomes, such as chronic kidney disease (CKD) and tumor features, has had limited representation in such tools [9-11].

Several compelling reasons exist for exploring the development of a risk communication tool and its pilot testing among outpatients receiving kidney tumor treatment. First, there is a large amount of information regarding the diagnosis that patients may have difficulty understanding and remembering accurately in a single verbal discussion with a physician. Kidney tumors comprise a diverse group of different benign and malignant tumor types. Even among malignancies, there is a wide degree of variation in the potential to metastasize and cause cancer-related death [1,4,5]. Second, there are also additional tests (ie, imaging or biopsy) that can offer additional information about the potential of the patient's tumor to progress, and these also require explanation that may not be effectively described by a nonradiologist.

Management options that serve as alternatives to initial surgical resection have gained recognition in clinical practice as reasonable alternatives to the current standard of surgery depending on the patient's medical comorbidities and tumor features that affect the type of surgery recommended (partial or whole removal of the affected kidney). Partial nephrectomy is performed whenever possible to preserve some of the affected kidney but can still reduce kidney function, and baseline kidney disease is associated with worsened postoperative overall survival [12]. The guidelines of the American Urological Association do not describe specific criteria for offering these alternative forms of treatment [13,14]. Third, treatment-related consequences are important when selecting a treatment, and describing such complex medical consequences as CKD requires clear descriptions and ideally graphical representation. Fourth, this work aims to create a feasible model that, if effective, can be easily extended across diseases associated with possible personalized pathways of more testing options and delaying intervention when abnormalities are likely indolent, or initial selection of minimally invasive therapies. Thus, our goal is to assess the feasibility of use and preliminary effect of a web-based DA on treatment choice for patients with SKMs.

Methods

Study Design

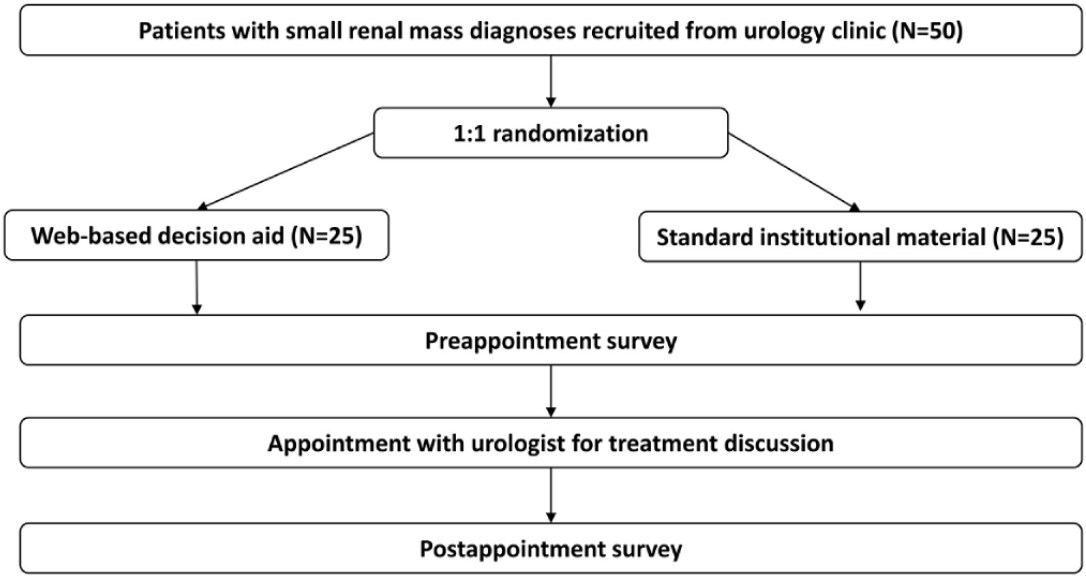
The study is a single-blinded pilot randomized controlled trial (RCT; ClinicalTrials.gov NCT05387863) that will evaluate the preliminary effect of a web-based DA compared with the existing institutional website on treatment decisions and decision-making measures. The DA or existing institutional educational material and questionnaires will be administered through a web-based, integrated, Health Insurance Portability and Accountability Act–compliant platform. Participants will be randomized to either receive the newly developed web-based DA or the standard institutional material.

The DA will include evidence-based risk communication about the diagnosis and treatment options, interfaced results of a decision-analytic model for tailored benefits or harms assessment based on the oncologic and nononcologic risk factors for mortality (eg, patient characteristics, comorbidities, and tumor imaging features), and brief individual values clarification to incorporate into decision-making for SKMs. We will compare the routine counseling for treatment decisions against this DA. The treatment strategies represented in the tool will include 4 options: the current standard of care (initial surgery with partial or radical nephrectomy), and the nonsurgical options of percutaneous ablation, active surveillance with biopsy, and active surveillance without biopsy.

Study Setting and Recruitment

This study will take place at 2 urology clinics within a large urban tertiary academic medical center in the northeastern United States. Patients will be identified via the clinic schedule in the electronic health record, where the reason for an upcoming first urologic consultation (ie, whether the patient has a newly diagnosed SKM) is specified. Study team members will then review the patient's medical record to ensure the SKM meets the size criteria (up to 4 cm), there is no regional or distant metastatic disease on imaging, and that no other exclusion criteria are present. Once identified, patients will be recruited via the telephone or email prior to their standard of care consultation with their urologist. They will have already received a diagnosis by routine communication with their care team. Patients will be aged 18 years or older and diagnosed with a localized renal tumor (clinical stage T1a) for which they have not yet received treatment. Other exclusion criteria are stage IV cancer of any type, vulnerable subjects, inability to understand English, and inability to provide informed consent. When a patient agrees to participate, a member of the study team will meet them in the urology clinic on our medical center's campus prior to their appointment to begin the study visit. The web-based DA will be administered to 25 patients, and the existing institutional website will be shown to 25 patients who provide informed consent. Patients will be randomized using a 1:1 allocation ratio (DA comprises standard institutional materials; see Figure 1) with a random sequence generated by a study team member to assign patients and with blinding of the investigators.

Figure 1. Patient randomization schema using 1:1 allocation to web-based decision aid or to standard institutional material.



The Web-Based Decision Aid (Intervention)

The web-based DA was created by an interdisciplinary committee beginning in 2020, including a diagnostic and interventional radiologist, urologists, internist, and experimental psychologists who agreed on essential design and content components. Through an iterative process, team members designed and tested the DA in small groups of SKM patients to continuously improve on its contents. In its nascent form, the DA was a printed booklet designed in accordance with the International Patient Decision Aid Standards [15]. Through focus groups and semistructured interviews with patients with SKM and 3 physicians, thematic analysis was also conducted to improve this prototype DA until the printed version was finalized. Upon identifying additional educational needs through knowledge items, the web version incorporated more graphics for explaining CKD, the impact of CKD on overall health, and R.E.N.A.L. Nephrometry scores—a standardized measure of anatomic complexity [16].

The web-based DA tool delivers information regarding SKMs, treatment options, and preparation for shared decisions to improve patient knowledge and provide tailored treatment options based on patient information. With the additional web-based graphics and values clarification, the tool may further improve upon initial findings that the booklet form of the DA resulted in more accurate understanding of risks associated with SKMs and each treatment option, and greater preference for nonsurgical initial approaches as compared to patients who received existing institutional educational materials [17].

The DA states the advantages and disadvantages of each treatment option and is designed to prepare for informed engagement in a treatment discussion with the urologists at the first clinical consultation after diagnosis of the mass. The DA tool is a set of web pages with 3 main sections (*About Small Kidney Masses*, *Treatment Options*, and *Find the Right Treatment for You*) and content covering cancer staging information, normal kidney function, chronic kidney disease, and a tool to provide tailored treatment recommendations (Figures 2 and 3). The first topic captures an overview of the kidney and its function, CKD and its progression, SKMs, the types of tumors (benign vs malignant) and how each type could progress, and the risk factors leading to kidney cancer. The second topic focuses on SKM management, with treatment

options ranging from active surveillance to minimally invasive procedures (percutaneous thermal ablation) to surgery. For each option, we provide an overview of how the treatment is performed including its benefits and potential effects on kidney function and key factors that could increase the risk of harm from treatment. All information is provided with images for clarification as needed, and educational content is written in consideration of literacy at an 8th grade reading level.

The third section of the web-based DA includes 5 questions on age, sex, known diagnosis of CKD and CKD stage, R.E.N.A.L. Nephrometry score, and a list of comorbidities for which patients indicate presence or absence. Any missing responses can result in a default answer that applies a normal baseline value (or minimum Nephrometry score) with instruction to discuss these factors and treatment options with their doctor. To facilitate shared decision making, patients are asked to rate the importance (scale of 1-5, with 5 being very important), of attributes of the treatment choices (possible advantages and disadvantages of each treatment option) and then to indicate the preferred treatment option at that time. These features will allow evaluation of the most common and important preferences in treatment decisions. Finally, the ratings for treatment attributes are presented along with the set of treatment choices that should likely be considered with the doctor, based on presence or absence of risk factors for poor surgical outcomes (Figure 4).

Figure 2. The landing page for the DA website contains a brief introduction of the contents patients will see while using the DA.

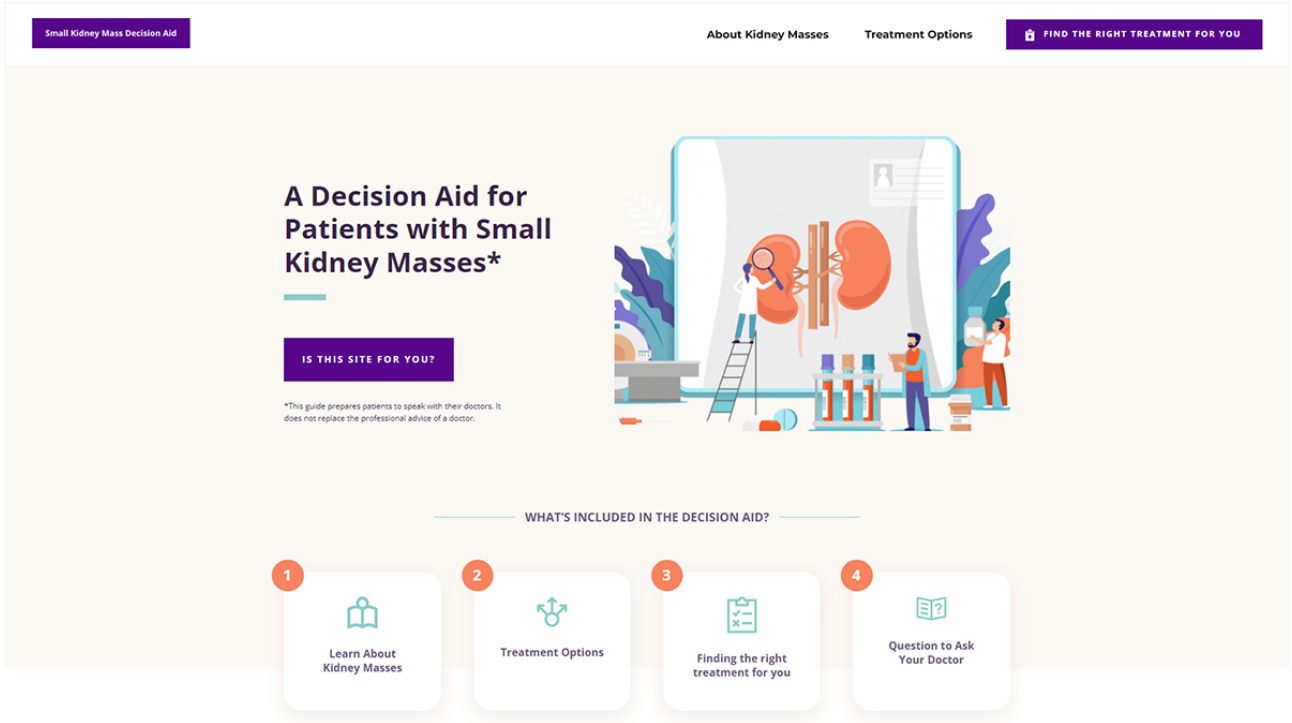


Figure 3. Screenshot of a page of the web-based decision aid providing information on one of the treatment options—percutaneous ablation.

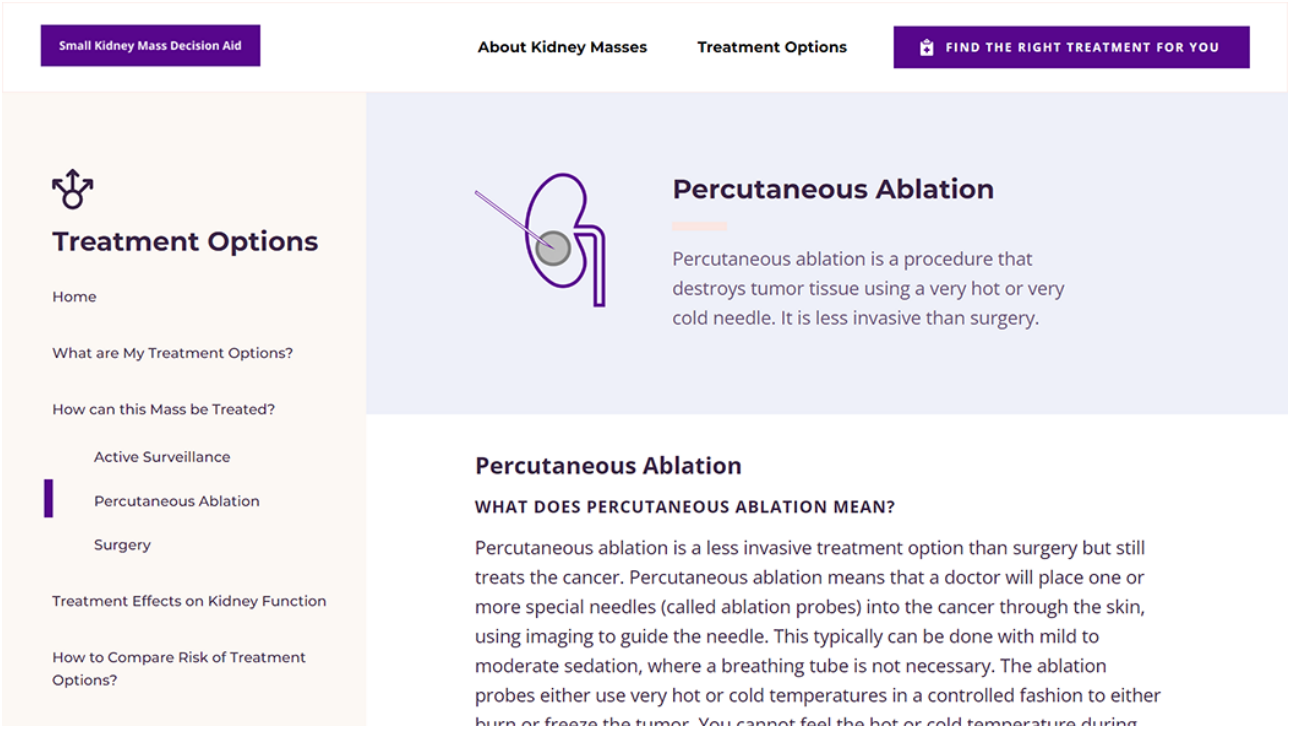
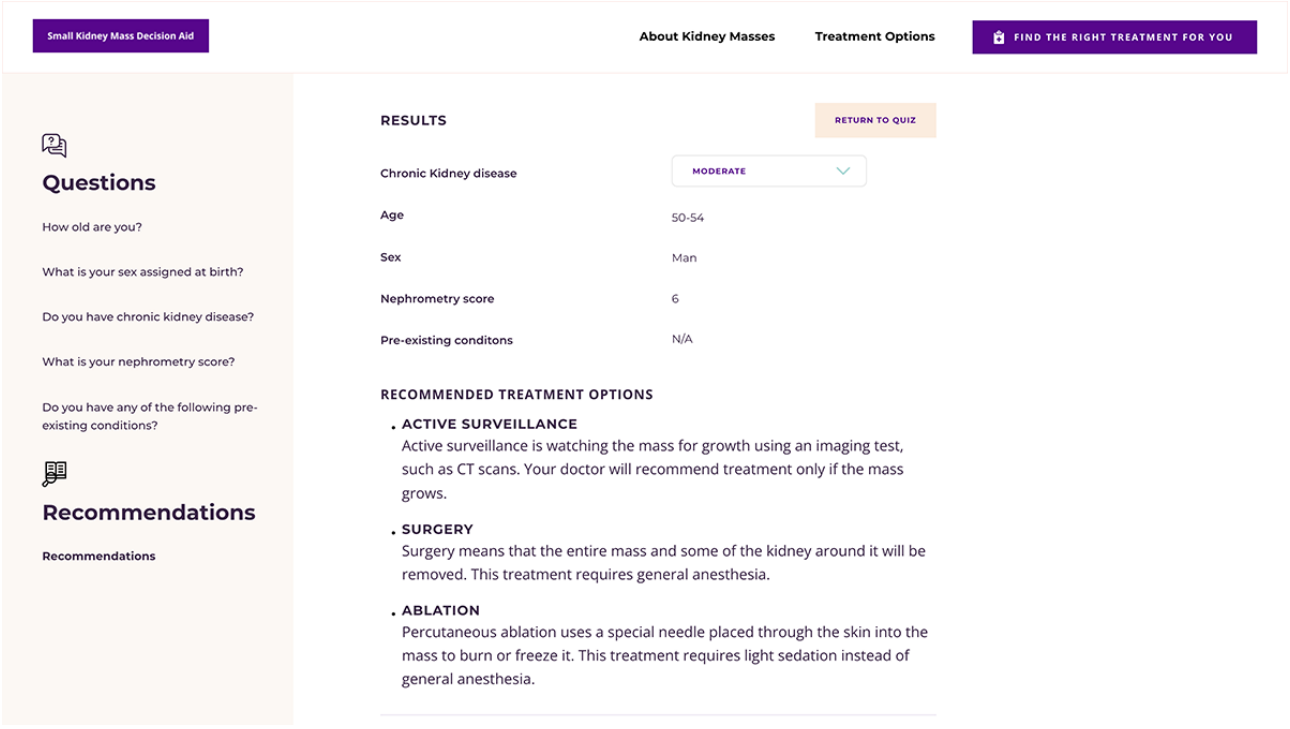


Figure 4. Screenshot of treatments to consider with providers after patients indicate responses regarding their age, health, and tumor characteristics. CT: computed tomography.



Procedure

Data time points comprise one visit for each participant. The study visit, including the patients' appointments with their urologists, will last approximately 2 hours. Patients will arrive for their regularly scheduled appointments 50 minutes early. Patients who agree to participate will go through the informed consent process with a member of the study team and will subsequently be randomized to receive the DA or the standard, web-based institutional pamphlet (Figure 1). Prior to their consultation with their urologist, they will answer brief surveys for demographics and literacy or numeracy [18-20]. They will then review the web-based DA or standard institutional material provided by the research team. The study team member will be available only for technical questions while reviewing the materials. Patients will then answer surveys about the material provided, their treatment preferences, and knowledge items (Multimedia Appendix 1) about SKMs' treatment options.

After reviewing the educational materials and answering the first sets of surveys, patients will attend their appointment with their urologist. Following their consultation, the patients will answer surveys about the visit and the decision-making process and will reindicate their desired treatment at that time.

In the following 3-6 months, a study team member will check patient medical records to assess what management option the patient undertook for the first 3 months after the initial consultation, kidney function at the clinically indicated follow-up visits (typically at least one blood test within 6 months regardless of the treatment), routine blood tests, and reports of tumor stage progression.

The questionnaires administered throughout the study, the web-based DA, and standard institutional website will be administered on electronic tablets while a member of the research team is present to answer technical questions about questionnaire functionality and website navigation problems. We will use the institutional Research Electronic Data Capture system to create and administer surveys [21,22]. An advantage of this software is its ability to create unique links leading to the DA website or the web-based institutional materials, creating a seamless integration of survey responses and DA use and responses. Patients will receive US $50 gift cards as compensation for time spent in review of the study materials.

Measures

Prior to reviewing the educational materials, participants will answer questionnaires to collect demographic information (sex, race and ethnicity, and educational attainment), self-described literacy abilities [18], numeracy abilities [19,20], and comfort with using different types of technology. A primary outcome for this pilot study is feasibility of viewing the web DA prior to the appointment, and thus the percentage of patients viewing most or all of the tool will be assessed. Participants will answer questions regarding SKM knowledge after presentation of the educational materials to assess the educational benefit of the DA versus the standard institutional materials. Participants will also indicate their preferred treatment. Just after the patient finishes the urologic consultation, an additional survey will be administered. In this postvisit survey, the questions will include the Decisional Conflict Scale, which consists of 16 prompts with a 5-point Likert scale ranging from 1="strongly disagree" to 5="strongly agree" to assess uncertainty in the decision, decision efficacy, and contributors to feelings of uncertainty [23,24]. A second survey assessing the shared decision-making (SDM) process scores will be administered to measure patients' ability to share during decision-making while considering each treatment's pros and cons [25]. In the postvisit survey, we ask participants again to indicate their preferred treatment. The measures used for our study analysis are provided in Table 1.

Renal function will also be recorded as an exploratory measure, as well as other major comorbidities represented in the Charlson comorbidity score [26], through a review of medical records for up to 6 months following a participant's completion of the study.

Table 1. Decision-making measures and their corresponding descriptions.

Measure	Description
3-item Subjective Numeracy Scale	Individual numeracy skill based on a summation of self-reported ratings of 3 items, including individual comfort to fractions, percentage, and numerical information, where the rating scale ranges from 1="not good at all" to 6="extremely good."
Decisional Conflict Scale (DCS)	Difficulty in decision-making based on a questionnaire consisting of 16 items with responses rated on a 5-point Likert scale ranging from 1="strongly disagree" to 5="strongly agree." To calculate DCS scores, we will convert the responses of 1 to 5, 2 to 4, and from 5 to 1 such that the DCS range is from 0="no decisional conflict" to 100="extremely high decisional conflict." DCS has 5 subscores: uncertainty, informed, values clarity, support, and effective decision subscores.
Uncertainty subscore	Measure of uncertainty or confidence in patient decision-making based on 3 items (items 10-12) from a 16-item questionnaire. The subscores are calculated by (1) summing, (2) dividing by 3, (3) deducting by 1, and (4) multiplying by 25.
Informed subscore	Measure of how well-informed patients are regarding treatment options based on 3 items (items 1-3) from a 16-item questionnaire. The subscores are calculated by (1) summing, (2) dividing by 3, (3) deducting by 1, and (4) multiplying by 25.
Values Clarity subscore	Measure of patient clarity in their preference regarding treatment benefits and harms based on 3 items (items 4-6) from a 16-item questionnaire. The subscores are calculated by (1) summing, (2) dividing by 3, (3) deducting by 1, and (4) multiplying by 25.
Support subscore	Measure of how much support or advice patients receive from others influence their decision based on 3 items (items 7-9) from a 16-item questionnaire. The subscores are calculated by (1) summing, (2) dividing by 3, (3) deducting by 1, and (4) multiplying by 25.
Effective Decision subscore	Measure of how effective or satisfied patients feel about their decision based on 4 items (items 13-16) from a 16-item questionnaire. The subscore is calculated by (1) summing, (2) dividing by 4, (3) deducting by 1, and (4) multiplying by 25.
Total scores	The total score is calculated by (1) summing, (2) dividing by 16, (3) deducting by 1, and (4) multiplying by 25.
Shared Decision-Making (SDM) Process scores	The degree of shared decision-making occurring during a treatment discussion between a patient and a clinician. SDM covers options, pros, cons, and preferences. The total score ranges from 0 to 4, where higher values represent a greater degree of shared decision-making.
Options	Measure of discussion on each of the available treatment options based on yes/no responses. To calculate the score, we will (1) convert "yes" to 1 and "no" to 0 for each question and (2) calculate the average of all relevant questions.
Pros	Measure of discussion on reasons patients should receive each of the treatment options based on the following responses: "a lot," "some," and "a little." To calculate the score, we will (1) convert "a lot," "some," and "a little" to 1, 0.5, and 0, respectively, for each question and (2) calculate the average of all relevant questions.
Cons	Measure of discussion on reasons patients should not receive each of the treatment options based on the following responses: "a lot," "some," and "a little." To calculate the score, we will (1) convert "a lot," "some," and "a little" to 1, 0.5, and 0, respectively, for each question and (2) calculate the average of all relevant questions.
Preferences	Measure of discussion on the selection of preferred treatment based on a yes/no response. To calculate the score, we will convert "yes" to 1 and "no" to 0.
Total scores	Total score is a summation of options, pros, cons, and preferences.

Sample Characteristics

We expect to enroll a total of 50 patients in this phase for the pilot trial. We expect that more adult men than women (approximately 60% men vs 40% women) will participate in this study based on the biologically higher incidences of kidney tumors in men. Based on previous research at our institution, we expect our sample to be approximately 25% Hispanic or Latino and approximately 25% Black or African American.

Data Analysis

Demographics, literacy and numeracy, technology use, and both pre- and postconsultation treatment preferences will be compared between the DA and institutional educational material groups using the Mann-Whitney test for continuous variables. We will also use a Fisher exact test for proportions (R version 4.0.5 [27]) with the mid-p adjustment for a 2 × 2 contingency table (exact2x2 package [28]) and with the ordinary *P* value for an r × 2 contingency table where r>2 [27]. Missing responses will be excluded from the analysis. All statistical tests will be

conducted at a 2-sided 5% comparison-wise significance level without adjustments for the number of comparisons.

Ethics Approval

The initial phases of DA development consisting of focus groups, semistructured interviews, and initial usability testing of the printed DA with patients with SKM), as well as the current phase pilot RCT protocol were approved by the New York University Grossman School of Medicine's Institutional Review Board (s16-010008 and s21-01670).

Results

The pilot RCT using the web-based DA was funded by the National Cancer Institute on August 10, 2021. After testing the web tool, enrollment will begin on August 29, 2022. We estimate recruitment and data collection to be completed by December 31, 2022, with analysis completed by January 30, 2023.

Discussion

Principal Findings

The study aims to evaluate the feasibility of administering of a web-based DA in the clinic and assessing its effects on decision-making compared with an existing institutional website explaining treatment outcomes of patients with SKMs. We anticipate that the web-based DA will be a feasible intervention to enhance patient knowledge of SKMs, with >80% of participants viewing all of the tool and DA recipients having higher knowledge scores. Early-stage data will be collected on surgical or nonsurgical treatment selection, with the expected outcome of fewer DA recipients choosing surgery as an initial treatment option compared to recipients of the standard institutional material, though the pilot will be underpowered to detect a difference. We will conduct comparative evaluation of the knowledge of patients, decision satisfaction, decisional conflict, and shared decision-making as secondary measures, with expected increases in knowledge, decision satisfaction, and shared decision-making and decreases in decisional conflict among DA recipients.

Strengths and Limitations

This study is the first example of a web-based DA for patients with SKMs that incorporates personalized risk-based information to guide treatment decisions. The rigorous approach to evaluating this intervention will pave the way for larger studies that aim to evaluate such web-based tools for patient viewing prior to a discussion with their providers about choosing a management approach. For incidental nodules in particular, accurate understanding of risk associated with the lesion itself (ie, metastasis and cancer-specific death), even if representing cancer, and the risks and benefits of treatment options are key to making decisions that are congruent with the degree of mortality risk. The DA was thus designed to allow patients with SKMs (nearly all incidentally detected) to understand their condition in an interactive, concise manner that facilitates better understanding of their options prior to their discussion with a urologist.

Initial usability testing in phase 2 informed an estimated review time of the given materials in under 30 minutes [17]. Patients who received the DA were more likely to self-report reviewing the DA completely than those who received the standard pamphlet [17], supporting the likelihood of viewing the web version of the tool, indicating that the DA is easily accessible to most populations and is not expected to be burdensome.

There are limitations to our proposed pilot trial, including the relatively small sample size for this initial evaluation of the web-based DA. The pilot RCT will be underpowered for detecting anticipated differences in surgical versus nonsurgical treatment selection with the use of a DA. There are elements of limitations inherent to more pragmatic trial designs, such as the ability of patients to access the tool on the internet with minimal usage direction by clinical staff instead of a highly controlled teaching session, self-report of the amount of content viewed in the DA, and minimal preparatory information or training of patients before using the tool. These elements were allowed for real-world evaluation of such decision support.

Several prior RCTs have been published on the role of DAs in prostate cancer treatment selection [9,11,29,30]. These trials have shown a broader range of treatment selected (ie, radiation therapy rather than prostatectomy) and increased decisional quality for patients. Similar to low-risk prostate cancer, treatment options for SKMs are associated with small differences in cancer progression between surgical treatment and nonsurgical therapy; thus, the trade-offs of choices warrant a DA.

Dissemination Plan and Future Directions

Results will be disseminated through peer-reviewed publications and conference presentations. Results from this pilot study will also be used to further inform the design of a larger multisite RCT for use in urologic clinics. The pilot randomized testing may lead to further revisions for the web-based DA, and ultimately a future trial would evaluate the differences in treatment choice (surgical vs nonsurgical treatment selection) and clinical outcomes.

Conclusions

While previous studies reported development of a DA for patients with SKMs, this study will address a gap in the existing literature. The newly developed web-based DA not only provides personalized, evidence-based risk communication, but also factors in tumor imaging features and potential comorbidities of surgical treatments as influencing factors in assessing patients' treatment preferences, which may increase patients' satisfaction with their treatment decisions. Eventually, a DA for patients with SKMs may show similar impact on initial surgical treatment as prior trials on DAs for prostate cancer, with accompanying increases in SDM and decisional quality. If the web-based DA is demonstrably effective in increasing patient knowledge about their treatment options and in reducing decisional conflict, it could be considered an adjunct more broadly for patients with SKMs.

Acknowledgments

The authors declare that they had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis. This work was supported by the National Cancer Institute (PI Kang, K07CA197134, CA197134-05S1). SK also received grant support from the National Institutes of Health's National Institute of Dental and Craniofacial Research, support for travel and teaching from the Radiological Society of North America, and royalties from Wolters Kluwer for unrelated work. The remaining authors report no financial support for related work.

Data Availability

The data sets generated from this study will be available upon study completion from the corresponding author on reasonable request.

Authors' Contributions

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting or critical revision of the manuscript for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared

Multimedia Appendix 1
Original knowledge items for patients to answer after viewing the web-based decision tool.
[PDF File (Adobe PDF File), 45 KB - resprot_v11i9e41451_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 359 KB - resprot_v11i9e41451_app2.pdf]

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Abbreviations

CKD: chronic kidney disease

DA: decision aid
RCT: randomized controlled trial
SDM: shared decision-making
SKM: small kidney mass

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Protocol

A Mobile Phone App for the Prevention of Type 2 Diabetes in Malaysian Women With Gestational Diabetes Mellitus: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Over 50% of women with a history of gestational diabetes mellitus (GDM) will develop type 2 diabetes (T2D) in later life. Asian women experience a disproportionate risk of both GDM and T2D compared to women from other ethnic backgrounds. Lifestyle interventions and behavior change can delay or even prevent the onset of T2D. We have developed a digitalized diabetes prevention intervention for the prevention of T2D in Malaysian women with GDM.

Objective: The protocol describes a randomized controlled trial (RCT) to test the feasibility of undertaking a definitive trial of a diabetes prevention intervention, including a smartphone app and group support. Secondary aims are to summarize anthropometric, biomedical, psychological, and lifestyle outcomes overall and by allocation group, and to undertake a process evaluation.

Methods: This is a two-arm parallel feasibility RCT. A total of 60 Malaysian women with GDM will be randomized in the antenatal period to receive the intervention or standard care until 12 months post partum. The intervention is a diabetes prevention intervention delivered via a smartphone app developed based on the Information-Motivation-Behavioral Skills model of behavior change and group support using motivational interviewing. The intervention provides women with tailored information and support to encourage weight loss through adapted dietary intake and physical activity. Women in the control arm will receive standard care. The Malaysian Ministry of Health's Medical Research and Ethics Committee has approved the trial (NMRR-21-1667-60212).

Results: Recruitment and enrollment began in February 2022. Future outcomes will be published in peer-reviewed health-related research journals and presented at national, regional, or state professional meetings and conferences. This publication is based on protocol version 2, January 19, 2022.

Conclusions: To our knowledge, this will be the first study in Malaysia that aims to determine the feasibility of a digital intervention in T2D prevention among women with GDM. Findings from this feasibility study will inform the design of a full-scale RCT in the future.

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KEYWORDS

gestational diabetes mellitus; diabetes prevention; randomized controlled trial; mobile app

Introduction

Background

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. The condition is defined as glucose intolerance resulting in hyperglycemia, which is first recognized in pregnancy and resolves after delivery [1]. Prevalence rates vary considerably from 1.8% to 31.5% depending on the diagnostic criteria used and the population studied [2]. Globally, prevalence is increasing, mirroring general upward trends in noncommunicable disease, maternal age, and obesity prevalence. In the short term, GDM is associated with obstetric complications including pre-eclampsia and cesarean section [3,4], and undesirable perinatal outcomes including large birth weight and shoulder dystocia [5]. In the long term, GDM is associated with increased maternal risk of GDM recurrence in subsequent pregnancies [6], cardiovascular disease [7], and type 2 diabetes (T2D) [8], while children of mothers with GDM are at increased risk of obesity, hypertension, and T2D later in life [9]. GDM is the single strongest population predictor of T2D. Approximately 50% of mothers with GDM will develop diabetes within 10 years [8,10,11].

People of Asian ethnicity are at higher risk of developing T2D than people of White ethnicity. More than 60% of people with T2D live in Asia [12,13] with prevalence rates estimated to increase by more than 150% between 2000 and 2035 [13]. Among Asian countries, Malaysia has one of the highest comparative prevalence rates of T2D at 20.8% [14] compared with other neighboring countries such as Singapore (12.8%) and Thailand (8%) [15]. Malaysia has a multiethnic society including three major ancestral groups (Malay, Chinese, and Indian), with Malaysian Indian people having the highest prevalence of T2D (28%), followed by Malay people (19%) and Chinese people (9%) [16]. Women in Malaysia also experience GDM at disproportionate rates in comparison to women from other ethnic groups. The incidence of GDM in Malaysia was 7.7% in 2016 and 9.3% in 2017 [17].

Evidence from landmark studies has shown that healthy lifestyle interventions and behavior change can delay or even prevent the onset of T2D. The Finnish Diabetes Prevention Study and the Diabetes Prevention Program both demonstrated a 58% reduction in the incidence of T2D in individuals with impaired glucose tolerance after 3 years of lifestyle interventions focused on diet and physical activity [18,19]. Similar findings have been observed in an Asian setting. The Da Qing Diabetes Prevention Study, after 6 years of lifestyle intervention, was associated with reduced incidence of T2D by 31%, 46%, and 42% in the groups of diet, exercise, and diet plus exercise, respectively [20], and benefits extended over 20 years after the intervention was discontinued [21].

However, evidence to support the efficacy of prevention interventions in women with a history of GDM is not clear. Subgroup analysis of the landmark Diabetes Prevention Program showed a 50% reduction in T2D incidence in women (n=350) with prior GDM in the previous 10 years [22]. Further, a meta-analysis of randomized controlled trials (RCTs) on the effectiveness of lifestyle interventions in the prevention of T2D in women with previous GDM demonstrated a 25% reduction in diabetes risk [23]. Small but statistically significant reductions in weight, BMI, and waist circumference were reported with longer periods of intervention [23]. Several barriers have been identified to lifestyle interventions in postpartum women with recent GDM, including tiredness, lack of time, competing work and family demands, childcare, and cultural expectations [24,25].

Mobile health (mHealth) is a rapidly growing field of public health, defined as the use of mobile phones and other wireless technology to support health objectives [26]. Due to the increasing ownership of smartphones, significant numbers of mHealth apps have been developed [27]. Pregnant and postpartum women are increasingly using such technologies as sources of health information and services for pregnancy self-care and infant care [28,29]. Smartphone apps can provide a novel way to deliver health interventions during this life stage, as they can address previously mentioned barriers experienced by women due to their flexibility and home-based approach.

The Malaysian Gestational Diabetes and Prevention of Diabetes Study

The Malaysian Gestational Diabetes and Prevention of Diabetes Study (MY GODDESS) aims to reduce the risk of T2D in women with GDM in Malaysia. The project consists of two work streams. The first work stream involves a systematic review to synthesize process evaluations of RCTs on diabetes prevention interventions for women with current or a history of GDM [30], focus groups using qualitative methods to identify

barriers and facilitators to uptake of DPI [31], focus groups to model the diabetes prevention intervention, and development of an interactive smartphone app. The second work stream involves a feasibility RCT of the developed diabetes prevention intervention for women with GDM in Malaysia. This paper presents the protocol for the MY GODDESS feasibility RCT.

The overall aim of the RCT is to test the feasibility of undertaking a definitive trial of a diabetes prevention intervention including a smartphone app and group support over 15 months in women with GDM from randomization in the antenatal period to 12 months post partum.

Methods

This protocol was designed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013. A SPIRIT study timeline (Table 1) and SPIRIT checklist (Multimedia Appendix 1) are provided.

Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) timeline for the trial.

	Study period								
	Enrollment	Randomization	Postrandomization					Ongoing	Close-out
	$-t_1$	0	t_1	t_2	t_3	t_4	t_5		
Enrollment									
Eligibility screen	✓[a]								
Informed consent	✓								
Allocation		✓							
Intervention									
Standard care + app		✓							
Standard care		✓							
Assessments									
Demographic									
Date of birth		✓							
Ethnicity		✓							
Postcode of residence		✓							
Education level		✓							
Employment status		✓							
Household income		✓							
Gravidity		✓							
Parity		✓							
Previous pregnancy with GDM[b]		✓							
Anthropometric									
Body weight		✓	✓	✓	✓	✓	✓		
Height		✓							
BMI		✓	✓	✓	✓	✓	✓		
Body fat percentage		✓	✓	✓	✓	✓	✓		
Biomedical									
Systolic and diastolic blood pressure		✓	✓		✓		✓		
Total cholesterol		✓	✓		✓		✓		
LDL[c] cholesterol		✓	✓		✓		✓		
HDL[d] cholesterol		✓	✓		✓		✓		
HbA_{1c}[e]		✓	✓		✓		✓		
Fasting plasma glucose		✓	✓		✓		✓		
OGTT[f] 2 hours postprandial					✓		✓		
Insulin resistance (HOMA-IR[g])		✓	✓		✓		✓		
Psychological									
SEE[h]		✓			✓		✓		
Maternal Antenatal Attachment Scale		✓			✓		✓		
Maternal Postnatal Attachment Scale					✓		✓		
PHQ-9[i]		✓			✓		✓		
Lifestyle									

	Study period								
	Enrollment	Randomization	Postrandomization					Ongoing	Close-out
	$-t_1$	0	t_1	t_2	t_3	t_4	t_5		
24-hour dietary recall		✓			✓		✓		
SF-IPAQ[j] score		✓			✓		✓		
Step count		✓			✓		✓		
Smoking status		✓							
Alcohol		✓							
Infant feeding practices					✓		✓		
Clinical variables									
Maternal medical information									
Hypercholesterolemia				✓					
Hypertension				✓					
Pre-eclampsia				✓					
Maternal pregnancy and birth data									
Place of antenatal care				✓					
Date of delivery				✓					
Place of delivery				✓					
Delivery method				✓					
Pregnancy complications				✓					
Birth complications				✓					
Breastfeeding status				✓					
Neonatal data									
Birth weight				✓					
APGAR[k] score				✓					
Congenital anomaly				✓					
Congenital pneumonia/heart defects				✓					
Admission to neonatal intensive care, special care, or qualified on ward				✓					
Length of stay				✓					
Feasibility outcomes								✓	
Process measures				✓	✓			✓	

[a]Included at this time point.

[b]GDM: gestational diabetes mellitus.

[c]LDL: low-density lipoprotein.

[d]HDL: high-density lipoprotein.

[e]HbA_{1c}: hemoglobin A_{1c}.

[f]OGTT: oral glucose tolerance test.

[g]HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

[h]SEE: Self-Efficacy for Exercise.

[i]PHQ-9: Patient Health Questionnaire.

[j]SF-IPAQ: Short-form International Physical Activity Questionnaire.

[k]APGAR: appearance, pulse, grimace, activity, and respiration.

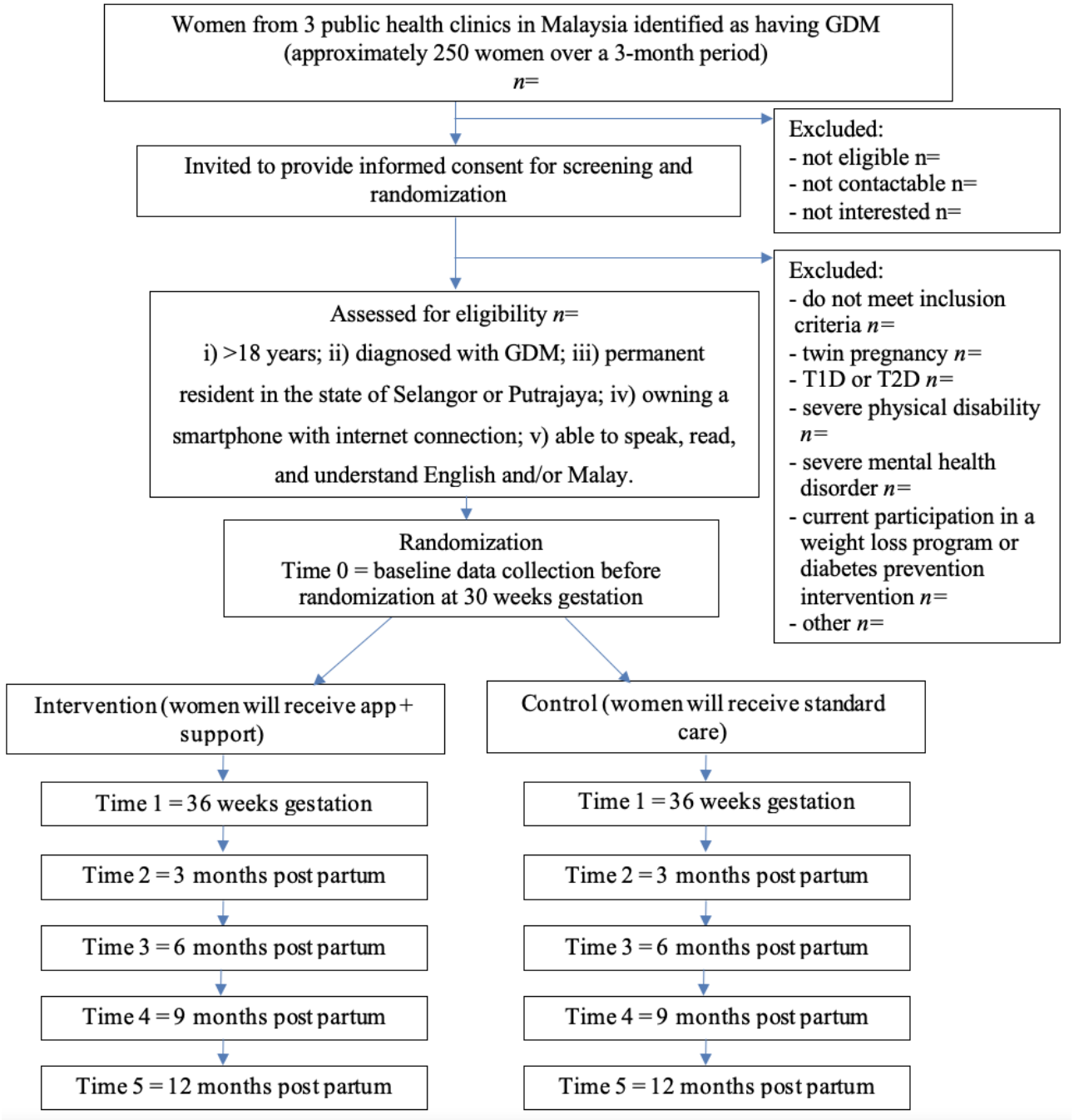
Ethics Approval

Ethics approval was granted by Malaysian Ministry of Health's Medical Research and Ethics Committee (NMRR-21-1667-60212). The study is registered on ClinicalTrials.gov (NCT05204706).

Study Design

This is a two-arm, parallel, open-label feasibility RCT with an allocation ratio of 1:1 for intervention and control arms. The two arms are the intervention arm comprising of a smartphone app and group support delivering a lifestyle intervention and a control arm consisting of standard care. The flow of participants through the study is presented in Figure 1.

Figure 1. Study flow diagram. GDM: gestational diabetes mellitus; T1D: type 1 diabetes; T2D: type 2 diabetes.



Note: Data collected at follow-up time points are anchored around the date of birth to ensure that every participant is at the same stage biologically for the follow-up. The date of data collection will be used to adjust for time from randomization.

Study Setting

Participants will be recruited from three public health clinics within the states of Selangor and Putrajaya in Malaysia. Each clinic provides care for around 100,000 people. In these health clinics, the average total daily reported GDM cases range from 5 to 10 cases, with an annual prevalence of 700 to 1000 women.

Eligibility Criteria

Inclusion Criteria

Women will be eligible for recruitment if they meet the following criteria: older than 18 years; diagnosed with GDM defined using fasting blood glucose >5.1 mmol/1 or 2-hour postprandial >7.8 mmol/1, which are the standard guidelines for diagnosis of GDM in Malaysia [32]; permanent resident in the state of Selangor or Putrajaya; registered in one of the study health clinics; owning a smartphone (iOS 11 or Android 7) with internet connection; and able to speak, read, and understand English or Malay.

Exclusion Criteria

Women will be excluded if they meet any of the following criteria: are having a twin pregnancy, have type 1 or 2 diabetes, have a severe physical disability that would prevent any increased uptake of physical exercise, have a severe mental health disorder (psychosis, bipolar, substance dependence, or active suicidal ideation), or are currently participating in a weight loss program or diabetes prevention intervention. For women who decline to participate, their age, parity, BMI, ethnic origin, education level, occupation, and household income will be recorded if permission is granted.

Recruitment and Informed Consent

The study population will be all women with GDM in Selangor and Putrajaya, Malaysia. In Malaysia, pregnant women are screened for GDM in the first trimester (if they have risk factors) or in the second trimester between 24 and 28 weeks gestation using the 2-hour oral glucose tolerance test (OGTT) [32]. The results are recorded in an antenatal register. Potentially eligible women will first be identified from this register by clinic staff and introduced to a research team member. The research team member will provide women with a study brochure, a verbal description of the study, and an opportunity to ask questions about the study. Women will be given at least 1 week to consider their participation. If the participant agrees, informed consent and screening for eligibility to participate in the study will be obtained. Recruitment will be adapted to be conducted remotely depending on the nature of any COVID-19 restrictions in place at time of recruitment.

Baseline Measures Collected Before Randomization

Sociodemographic

Date of birth, ethnicity, postcode of residence, education level, occupation, household income, gravida, parity, and number of previous GDM pregnancies.

Anthropometric

Body weight will be measured in light clothing, without shoes, to 0.01 kg, and height to 0.1 cm using a stadiometer. Height will be measured without shoes and socks using a stadiometer (SECA 213) to the nearest 0.1 cm. The BMI will be calculated as weight (kg) / height^2 (m^2). Body fat percentage will be assessed using bioimpedance analysis (Tanita RD-545 InnerScan Pro).

Biomedical

Systolic and diastolic blood pressure (mmHg) will be measured using a digital Omron HBP-1120 monitor using standardized procedures of the average of two readings taken 1 minute apart while seated. Blood venous samples will be collected via venipuncture. The lipid profile (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol) will be measured using an Advia 2400 (Siemens Diagnostics) analyzer, detection limit 0.1 mg/L and 0.01 mmol/L, respectively. Hemoglobin A_{1c} (HbA_{1c}) level (mmol/mol) and fasting blood glucose (mmol/l) will be measured by affinity chromatography using the Primus Ultra 2 analyzer (Primus Corporation) and an Advia 2120 analyzer (Siemens Diagnostics), respectively. For the OGTT, participants will be asked to fast for 8 hours, after which fasting blood glucose and fasting insulin will be measured, then the participant will be invited to drink 75 g of glucose in 200 ml of water, and 2 hours later the blood glucose will be measured. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) will be calculated by multiplying fasting plasma glucose (mmol/l) by fasting serum insulin (U/mL) divided by 22.5.

Psychological

Self-efficacy will be measured using the Self-Efficacy for Exercise (SEE) Scale, which comprises 18 items [33]. Response options are presented on a Likert scale from 0 to 100, ranging in 10-unit intervals from 0 (cannot do) through intermediate degrees of assurance, 50 (moderately certain can do), to complete assurance, 100 (highly certain can do). The scale is scored by summing the numerical ratings for each response and dividing by the number of responses. Higher scores indicate higher self-efficacy for exercise. The mother-infant relationship will be assessed in the antenatal period using the Maternal Antenatal Attachment Scale, which comprises 19 items with response options presented on a 5-point Likert scale [34]. Higher scores are indicative of stronger attachment, but a specific cutoff is not provided [34]. Depressive symptoms will be measured using the Patient Health Questionnaire (PHQ-9), comprising 10 items scored on a 4-point Likert scale with a score range from 0 to 27 and higher scores representing worse depressive symptoms and a score 10 representing caseness for diagnosis of depressive disorder [35].

Lifestyle

Dietary intake will be assessed using standardized multiple-pass 24-hour dietary recall for 3 days (2 weekdays and 1 weekend day) as it is considered an objective and reliable measure of change in intervention studies [36]. Clinical researchers will be trained to follow a standardized protocol, ask neutral probing questions to encourage recall of food items, and taught about different methods of food preparations and brands in different cultures. Physical activity will be measured using the Short-form International Physical Activity Questionnaire (SF-IPAQ), which

comprises seven items to capture average daily time spent sitting, walking, and engaging in moderate and vigorous physical activity over the last 7 days [37]. Step count will be measured using inbuilt features of the patients' own smartphone; the previous 7-day average will be used. Smoking status will be measured using a single item measure with response options including current smoker, previous smoker, and never smoked. Alcohol intake will be measured using the first question of the Alcohol Use Disorders Identification Test [38].

Randomization

Women who meet study inclusion criteria and consent to study participation will be randomized using simple block randomization to two groups. The randomization system will be set up online using the system Sealed Envelope [39]. The randomization list will be generated by clinical research unit (CRU) officers prior to the first participant's baseline visit at 30 weeks of pregnancy, using random permuted blocks of 2 and 4 to treatment A or B in a ratio of 1:1 to ensure that the groups are balanced periodically. Once the randomization list has been generated, access to the list will be password protected. Only CRU officers will have access to the list and will be responsible for randomizing participants. At 30 weeks of pregnancy during the baseline visit, once the consent form has been signed, eligibility has been confirmed, and baseline assessments have been completed, a research member in the clinic will call CRU officers to obtain group allocation. The CRU officers will access the randomization list the same day to obtain the allocation. Recruitment and randomization will be ongoing until each arm of the study comprises 30 participants.

Trial Arms

Control Arm: Standard Care

Women allocated to the control arm will receive standard care and no intervention. This includes self-monitoring blood glucose and lifestyle advice (diet, physical activity, optimal body weight) by a multidisciplinary team.

Intervention Arm: Mobile App + Group Support

Women allocated to the intervention arm will receive access to a smartphone app called MyManis (the English meaning of MyManis is *my sweet baby)* and group support.

MyManis App

The development of the app was guided by the Information-Motivation-Behavioral Skills (IMB) model of behavior change [40]. The IMB model identifies three core determinants of the initiation and maintenance of health behaviors: accurate information that can be readily translated into health behavior performance (ie, knowledge), motivation both personal and social to act on such information, and behavioral skills to execute the health behavior effectively and confidently. The constructs of the model are supported in the literature to improve healthy lifestyle behaviors and have been tested and used successfully in diabetes management [41-43], obesity prevention [44], and improving dietary and physical activity behaviors [45,46].

Participants randomized to the intervention will receive a brochure outlining the app features and a step-by-step guide on how to download the app and set up an account. A link to download the app via SMS text message will also be sent to participants for convenience. Once the app has been downloaded, participants will be invited to set up an account by inputting their name, date of birth, current week of gestation, height, and weight. Once completed, this will give them full access to the app. The app content is presented under six main tabs:

1. Home page: featuring weekly motivational and educational blog posts
2. Information: comprising clinical information about GDM and T2D including definitions, causes, consequences, and management
3. Diet: providing women with information on healthy eating including understanding relative amounts of the three main macronutrients using the Healthy Plate Method and information on healthy food swaps. Women will be provided with a series of recipes that reflect Malay, Indian, and Chinese ethnicities. Recipes will be grouped into breakfast, lunch, and dinner, and will be tailored according to the participants' nutritional requirements (based on BMI derived by the participant's log in details).
4. Exercise: comprises a weekly program of exercise tailored to pregnancy and the postpartum stage. Exercise programs are presented using visual aids including images and short videos. The focus will be on increasing step count, as walking is the most culturally appropriate activity in Malaysia. Safety precautions, including pre-exercise screening, tips for before/after the exercise including warm-up and cooldown, and monitoring the exercise's intensity using target heart rate calculation and Borg Scale are also incorporated in the app.
5. Well-being: providing information in relation to personal well-being in both the antenatal and postnatal period
6. GDM monitoring: allowing women to store personal information, blood glucose readings, and antenatal and postnatal appointment notes

The app is available to women in both Malay and English

Peer Support

Women will be invited to join group peer support. This will consist of 1-hour sessions with a group of 10 women meeting weekly via a virtual group chat function and communication of SMS text messages supporting each other during the week. Group support will be facilitated by a dietician trained in motivational interviewing (MI).

Technical Care

Women will be notified via SMS text message if an update of the app is required. During follow-up visits to their health clinic, women will be provided with in-person app support if required. Women who have not accessed the app for over a 2-week period will be flagged, and a notification will be sent via the app to motivate engagement.

Data Collection

Feasibility Outcomes

The primary feasibility outcomes are to estimate the proportion of women who were randomized out of those identified from the clinical registers (study population); the proportion of women who take up the intervention out of those in the intervention arm, to be defined by measures of digital analytics (data will be collected on date of log in, time spent on each component of the app, and total time spent on the app); and the proportion of women who are withdrawn or lost to follow-up out of those randomized (ie, those who provide no primary or secondary outcome data).

The secondary feasibility outcomes are to estimate the proportion of women identified from clinical registers (study population) who give consent for screening for eligibility; the proportion of women who were randomized out of those eligible to participate; the proportion of those who completed the secondary outcomes at follow-up out of those randomized; and the number of women randomized per month overall and per month per study site.

Secondary Outcomes

Anthropometric

Anthropometric outcomes will be collected antenatally at 36 weeks gestation (time 1), and at 3 (time 2), 6 (time 3), 9 (time 4), and 12 (time 5) months post partum. They include weight (kg), height (cm; at time 1 only), BMI (kg/m2), and body fat percentage.

Biomedical

Biomedical outcomes will be collected antenatally at 36 weeks gestation (time 1) and at 6 (time 3) and 12 (time 5) months post partum. They include systolic and diastolic blood pressure (mm Hg), total cholesterol (mmol/L), LDL cholesterol (mmol/L), HDL cholesterol (mmol/L), HbA_{1c} (mmol/mol), fasting plasma glucose (mmol/L), OGTT (mmol/L; time 3 and 5 only), and insulin resistance (HOMA-IR).

Psychological

Psychological outcomes will be collected at 6 (time 3) and 12 (time 5) months post partum. They include self-efficacy (total SEE score), mother-infant relationship (total Maternal Postnatal Attachment Scale score), and depressive symptoms (total PHQ-9 score).

Lifestyle

Lifestyle outcomes will be collected at 6 (time 3) and 12 (time 5) months post partum. They include dietary intake (standardized multiple-pass 24-hour dietary recall), physical activity (total SF-IPAQ score), step count (mean steps, inbuilt smartphone function), and infant feeding practices (total score).

Process Evaluation Outcomes

A mixed methods six-component process evaluation framework will be used. Data collection methods for each component of the process evaluation are described below.

Recruitment

- Participant recruitment flow; number of eligible, consented, screened, enrolled, and randomized; reason for nonparticipation or exclusion
- Participant characteristics, sociodemographic data
- Recruitment strategy, description of recruitment pathways into MY GODDESS

Dose delivered

- Total number of MyManis app downloads
- Total number of group support sessions delivered

Dose received

- Digital analytics of MyManis app including date of log in, total number of log ins per month, length of log in, time spent on each component of the app
- Group support attendance logs

Program implementation/fidelity

- IT logs of the MyManis app will be collated on technical issues reported when using the intervention
- Assessment of competency of MI-trained dieticians in delivering group support

Provider experience

- Semistructured interviews with clinical research members who were responsible for participant recruitment and MI-trained dieticians who were delivering group support. Interviews will be conducted at the conclusion of the study and guided by an interview schedule.

Participant experience

- Semistructed interviews to understand participant experiences of the trial, satisfaction, and acceptability (women in the intervention arm only). Data will also be collected on the acceptability of assessing the mother-infant relationship via observation from participants perspectives at 3 months. Mother-infant relationships will be assessed via video recording obtained either at the clinic or via videoconference at the woman's home. The recordings will aim to include both the mother's and baby's faces to enable coders to adequately visualize subtle movements, facial expressions, and vocalizations. Mothers will be advised to "talk and play with your baby as you normally would" prior to the recording. Recordings will be uploaded to a password - protected computer and assessed and coded based on the Child Adult Relationship Experimental Index [47].
- Satisfaction survey: a purpose-designed survey regarding acceptability and perceived usefulness of the MyManis app

Clinical Variables

The following maternal and neonatal variables will be collected to describe the sample and the potential attrition and generalizability of a larger trial in this population. These variables will be collected at 3 months post partum (time 2) from postnatal records by a research team member. While we will not statistically assess them as such in this feasibility study, these variables may also be potential predictors or modifiers of postpartum outcomes at the later time points, which we may

need to consider for a larger trial. These include maternal medical data (gestational hypertension, gestational hypercholesterolemia, pre-eclampsia); maternal pregnancy and birth data (place of antenatal care, date of admission, date of delivery, place of delivery, date of discharge, delivery method, pregnancy complications, birth complications, or breastfeeding status on discharge); and neonatal data (birth weight; appearance, pulse, grimace, activity, and respiration [APGAR] score 5 minutes; congenital anomaly; congenital pneumonia/heart defects; admission to neonatal intensive care; special care or qualified on ward; length of stay).

Statistical Analysis

Sample Size

The aim is to recruit 30 women per arm, as this should be a large enough sample to estimate parameters such as the SD, which in turn can be used to estimate the sample size for an appropriately powered full-scale RCT [48]. This sample should also allow us to estimate the 95% CI for the primary feasibility outcome of the proportion randomized of those eligible, which we estimate will be approximately 10%, to a CI of within +/-8% [49]. This was calculated as:

Plans for Statistical Analysis

Data will be double entered into an SPSS (IBM Corp) data set, and data analysis for the study will be performed using SPSS. Statistical analysis and reporting will be presented in line with the CONSORT (Consolidated Standards of Reporting Trials) guidelines [50]. Statistical analyses will primarily be descriptive, aiming to provide estimates related to feasibility parameters and to help inform power calculations for a future definitive trial.

For the primary outcomes of feasibility, we will calculate proportions or rates and appropriate CIs. We will consider whether a larger phase III effectiveness trial is feasible based on three potential factors: ≥25% of eligible women agree to be randomized, ≥50% of women in the intervention arm take up the intervention, or there is less than <20% attrition (women withdrawn from the study or lost to follow-up).

The secondary outcomes will be summarized using appropriate summary statistics overall and by randomization arm at each outcome time point. Normally distributed continuous variables will be summarized using the mean and SD, skewed continuous variables using the median and IQR, and categorical variables using frequencies and proportions. As the majority of the secondary outcomes are continuous and repeatedly measured, we will estimate the mean difference between the arms using linear mixed effects models with a random intercept at the participant level. The repeatedly measured outcomes will be the dependent variables, with the independent variables being trial arm, time, and a trial arm by time interaction term to extract differences at different time points. We will use analysis of covariance models where possible (ie, also include the baseline measure of the outcome as another independent variable). Appropriate 95% CIs will be calculated for the overall group and by trial arm, but as this is a feasibility study, we will not compare these statistically nor provide a *P* value for comparisons between arms. We will also not impute missing data, although fitting the mixed effects models using maximum likelihood will help account for missing data under a missing at random assumption. Some variables (eg, PHQ-9 and conversion to T2D [HbA_{1c} of 48 mmol/mol]) will also be summarized (but not analyzed) as categorical variables based on their clinical cutoffs. Smoking status and the obstetric outcomes that will only be measured once will also be summarized rather than modeled.

In terms of the process evaluation, all quantitative data including checklists, logs, and feedback surveys will be analyzed using SPSS. Data will be analyzed descriptively by calculating total numbers and percentages and mean and SD or, if the data are not normally distributed, the median and range. Qualitative data will be analyzed using thematic analysis to identify, analyze, and report patterns (themes) within the data [51].

Overall, the proportion of missing data for individual items and measures will be examined to determine the suitability of instruments and the level of burden for a future full-scale trial. As this is a feasibility study, no subgroup analyses are planned.

Results

Recruitment and enrollment began in February 2022. Future outcomes will be published in peer-reviewed health-related research journals and presented at national, regional, or state professional meetings and conferences. This publication is based on protocol version 2, January 19, 2022.

Discussion

Overall Aim

The overall aim of this RCT is to test the feasibility of undertaking a definitive trial of a diabetes prevention intervention including a smartphone app and group support over 15 months in women with GDM from randomization in the antenatal period to 12 months post partum. Secondary aims are to summarize anthropometric, biomedical, psychological, and lifestyle outcomes overall and by allocation group, and to undertake a process evaluation. Prior to undertaking a definitive RCT of effectiveness, evidence is needed to determine if such a trial could be undertaken and confirm outcomes likely to be of the most importance in a future trial.

Strengths and Limitations

To our knowledge, this is one of the few feasibility RCTs to test a smartphone app designed to prevent T2D by intervening prior to birth for women with GDM. It is also the first RCT we know of developed specifically for the prevention of T2D for Malaysian women with GDM. Further, the primary ethnic groups in this study (Malay, Chinese, and Indian) are also the major ethnic groups in Asia, and therefore, if this intervention proves to be effective in the larger RCT, this may also be applicable to the wider Asian population. The limitations are that this a feasibility study and therefore not powered to test effectiveness at this stage.

Research and Clinical Implications

Findings from the feasibility RCT will assist in optimizing the diabetes prevention intervention smartphone app for a full-scale RCT. This will provide greater evidence and important knowledge in terms of diabetes prevention interventions using digital technology during this phase of a woman's life, not only in Malaysia but also worldwide, which is crucial for slowing the rise of T2D.

Acknowledgments

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Conflicts of Interest

NG has received consulting fees from Oviva and Fixing Dad for app development for type 2 diabetes management programs. All other authors declare no conflicts.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 54 KB - resprot_v11i9e37288_app1.docx]

Multimedia Appendix 2
Peer-review report 1 from the United Kingdom-Malaysia Health Research Partnership - UK Medical Research Council - Malaysia Partnerships and Alliances in Research (MyPAIR).
[PDF File (Adobe PDF File), 37 KB - resprot_v11i9e37288_app2.pdf]

Multimedia Appendix 3
Peer-review report 2 from the United Kingdom-Malaysia Health Research Partnership - UK Medical Research Council - Malaysia Partnerships and Alliances in Research (MyPAIR).
[PDF File (Adobe PDF File), 34 KB - resprot_v11i9e37288_app3.pdf]

Multimedia Appendix 4
Peer-review report 3 from the United Kingdom-Malaysia Health Research Partnership - UK Medical Research Council - Malaysia Partnerships and Alliances in Research (MyPAIR).
[PDF File (Adobe PDF File), 32 KB - resprot_v11i9e37288_app4.pdf]

Multimedia Appendix 5
Peer-review report 4 from the United Kingdom-Malaysia Health Research Partnership - UK Medical Research Council - Malaysia Partnerships and Alliances in Research (MyPAIR).
[PDF File (Adobe PDF File), 34 KB - resprot_v11i9e37288_app5.pdf]

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Abbreviations

APGAR: appearance, pulse, grimace, activity, and respiration
CONSORT: Consolidated Standards of Reporting Trials
CRU: clinical research unit
GDM: gestational diabetes mellitus
HbA_{1c}: hemoglobin A_{1c}
HDL: high-density lipoprotein
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance
IMB: Information-Motivation-Behavioral Skills
LDL: low-density lipoprotein
mHealth: mobile health
MI: motivational interviewing
MY GODDESS: The Malaysian Gestational Diabetes and Prevention of Diabetes Study
NHS: National Health Service
NIHR: National Institute for Health and Care Research
OGTT: oral glucose tolerance test
PHQ-9: Patient Health Questionnaire
RCT: randomized controlled trial
SEE: Self-Efficacy for Exercise
SF-IPAQ: Short-form International Physical Activity Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2D: type 2 diabetes

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Protocol

Effects of the Population-Based "10,000 Steps Duesseldorf" Intervention for Promoting Physical Activity in Community-Dwelling Adults: Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: The World Health Organization recommends 150 minutes of moderate to vigorous physical activity (PA), which translates to approximately 7000 to 10,000 steps per day for adults. In Germany, less than half of the population in this age range meets this recommendation, highlighting the need for population-based intervention approaches for promoting daily PA.

Objective: The complex community-based PA intervention "10,000 Steps Ghent," which was originally developed in Belgium and was shown to be effective for PA promotion, has been adapted for implementation and evaluation in 2 German cities. The original Belgian study is currently being replicated, and we aim to examine the effectiveness of the adapted intervention among adults living in intervention city districts in Duesseldorf when compared with those living in control city districts in Wuppertal, over the course of 1 year.

Methods: A controlled intervention trial examining the effects of an intervention addressing multiple levels (eg, individual level: website; organizational level: PA promotion in companies; community level: media campaigns and environmental changes) is being conducted. PA and various secondary outcomes will be assessed in 2 random samples of adults aged 25 to 75 years (n=399 in each city) at baseline and after 1 year.

Results: Funding for this study was obtained in March 2020. Recruitment for this study and baseline data collection were conducted from May 2021 to March 2022 (as of March 2022, 626 participants were enrolled in the study). The intervention will be implemented in Duesseldorf for 1 year from April 2022 onward, and follow-up assessments will be conducted, starting in May 2023 (until September 2023). Data analysis will be performed in fall 2023, and the results will be published in spring 2024.

Conclusions: To our knowledge, this is the first research project (currently underway in Germany) that is aimed at replicating the effects of a complex intervention for PA promotion that was previously shown to be effective in another European country.

Trial Registration: German Clinical Trials Register DRKS00024873; https://tinyurl.com/4c9e8azh

International Registered Report Identifier (IRRID): DERR1-10.2196/39175

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KEYWORDS

physical activity; population-based complex intervention; replication study; multilevel strategy

Introduction

Physical inactivity is the fourth largest risk factor for mortality worldwide and is one of the main drivers contributing to the etiology of noncommunicable diseases, such as type 2 diabetes, cardiovascular diseases, and certain cancers, which are preventable to a certain extent [1]. In Germany, an estimated 91% of deaths are due to these noncommunicable diseases [2]. It is widely known from previous research that the reduction of an inactive lifestyle [3] and an increase in regular physical activity (PA) leads to improvements in health, including physical, psychological, cognitive, and functional health over the entire life span [3,4]. A recently published cohort study found that among middle-aged men and women walking ≥7000 steps per day was associated with lower mortality rates compared with those walking ≤7000 steps per day [5].

The 2020 update of the recommendations for PA of the World Health Organization (WHO) and the American College of Sports Medicine states that "all adults should undertake 150-300 minutes of moderate-intensity, or 75-150 minutes of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity, per week" [6]. It has been noted that 150 minutes per week is the equivalent of 7000 to 10,000 steps walked per day [7,8]. In addition, muscular strengthening PA on at least two days per week is recommended to achieve the health benefits mentioned earlier and reduce the risks of chronic diseases (and the associated cost-intensive curative and rehabilitative measures) [6]. Furthermore, Rütten and Pfeifer [9] emphasize in the German national PA recommendations that adults should also avoid long, uninterrupted sitting phases and, if possible, interrupt sitting regularly with PA. According to the authors, "the greatest health benefits take place when individuals who were entirely physically inactive become somewhat more active. This means that all additional PA is linked to health benefits. Every single step away from physical inactivity is important, no matter how small, and promotes health" [9]. Currently, in Germany, only 43% of women and 48% of men aged ≥18 years meet the WHO and American College of Sports Medicine recommendations for PA [10], highlighting the need for population-based intervention approaches to promote daily PA.

The results of a meta-analysis suggest that engaging in population-based PA intervention approaches recommending the use of step counters to individuals is associated with an increase of approximately 2,000 steps per day [11]. The increase in step count is most pronounced among individuals participating in interventions aimed at promoting 10,000 steps per day [11]. Further, short-term pedometer walking interventions in primary care were associated with health benefits, such as fewer new cardiovascular events and fractures 4 years later [12]. In addition, a review and meta-analysis by Wahlich et al [13], including 9 studies in the review and 5 in the meta-analyses with follow-ups ranging from 12 months to 4 years (age range 18-89 years), revealed increases in steps per day at 12 months for intervention group participants compared with control group participants (mean difference 554, 95% CI 384-724 steps). There is also evidence of sustained intervention effects beyond 1 year. For the 2 outcomes, steps per day and minutes spent with moderate to vigorous PA (MVPA), maintained intervention effects for up to 4 years have been previously demonstrated [13].

Furthermore, previous research suggests that combining individual-level step-count monitoring interventions with environmental approaches to promote PA at the community level, such as signage in parks and other green spaces and media campaigns, in complex intervention approaches leads to increased PA at the population level [14,15]. De Cocker et al [14] implemented a multistrategy community-based intervention aimed at promoting PA in adults aged ≥18 years, which was an adaptation of the "10,000 steps Rockhampton" (Queensland, Australia) program [16,17]. This complex intervention consisted of a website to track steps, a local media campaign, environmental modifications, and the sale and loan of pedometers. Intervention effects were examined in a controlled intervention trial comparing PA at baseline and after 1 year in 872 randomly selected participants (aged 25-75 years) from an entire city (Ghent, Belgium) to 810 living in a comparison city (Aalst, Belgium) [14]. In this study, an increase of 8% in the number of individuals reaching the recommended 10,000 steps was observed in the intervention city at the 1-year follow-up compared with no increase in the comparison city. The average number of daily steps walked increased by 896 (n=660; 95% CI 599-1192) in the intervention compared with no increase in the comparison city (n=634; mean change −135; 95% CI −432 to 162). Self-reported PA confirmed this result.

A 4-year follow-up assessment of self-reported PA in 866 participants in the original trial revealed that daily step counts increased slightly in the intervention city and decreased in the comparison city. Interestingly, subgroup analyses yielded a positive interaction effect for healthier individuals and those with higher levels of education and a negative interaction effect for individuals with poor to moderate health. Thus, long-term intervention effects could not be detected at the 4-year follow-up in individuals living in the intervention city, but decreases in PA, which had been observed in the control group at the 1-year follow-up, could be prevented, except for the subgroup with poor to moderate health [15]. An evaluation of the statewide rollout of the PA intervention in Flanders compared a random sample of adults aged 25 to 75 years (n=881) with a historical control group including the baseline data of participants of both intervention and control groups of the original "10.000 Steps Ghent" intervention (n=1675). Dubuy et al [18] showed that the Flemish sample reported more walking, moderate and vigorous PA, as well as more work-related, leisure time, and household PA compared with the historical control group. In

addition, the pedometer-based daily step count was higher, and a greater proportion of Flemish individuals reached the goal of 10,000 steps per day, leading the authors of the study to the conclusion that statewide socioecological complex intervention approaches can impact PA in a large population [18].

Rütten and Pfeifer [9] formulated a need for similar local and regional population-based approaches for PA promotion in Germany, pointing out that complex interventions for PA promotion, including mass media campaigns, motivational decision aids, community-based multicomponent interventions, and environmental approaches, can effectively increase PA in the general population. Thus far, 5 large German research networks (Physical Activity and Health Equity: Primary Prevention for Healthy Ageing [AEQUIPA], CAPITAL4HEALTH, Health Literacy in Childhood and Adolescence [HLCA], PartKommPlus, and SMARTACT) have been working toward improving evidence-based health promotion and primary prevention in Germany, some of them with a special focus on population-based approaches for the promotion of PA [19]. For example, the Physical Activity and Health Equity: Primary Prevention for Healthy Ageing (AEQUIPA) research network [20] conducted theory-based and participatory empirical research on different aspects of PA and healthy aging between the years 2014 and 2022 [20]. In the PROMOTE subproject of the network, multicomponent web- and print-based interventions for the promotion of PA in adults aged ≥60 years were designed following a participatory approach. They were subsequently evaluated with varying follow-ups [21-25], and intervention content and materials are publicly available for adaptation and use in future interventions [26,27].

However, additional studies are still required to strengthen the evidence base regarding effective multilevel approaches for PA promotion in a broad segment of the German population spanning a wide age range. In addition, the implementation processes involved need to be better understood. Replicating the effects of complex interventions for PA promotion, previously shown to be effective in other European countries, may help identify effective intervention strategies for the German context. Therefore, the 2 aims of this study are to adapt the previously shown to be effective complex PA intervention "10,000 Steps Ghent" to the German context (name of the German intervention: "10,000 Steps Duesseldorf") and to evaluate its effectiveness for PA promotion in adults aged 25 to 75 years over the course of 1 year in 2 German cities in a controlled intervention study. The impact evaluation of the intervention is accompanied by a process evaluation monitoring implementation process as well as an economic evaluation, including cost-effectiveness and cost-utility analyses of the intervention. The specific research questions posed are as follows:

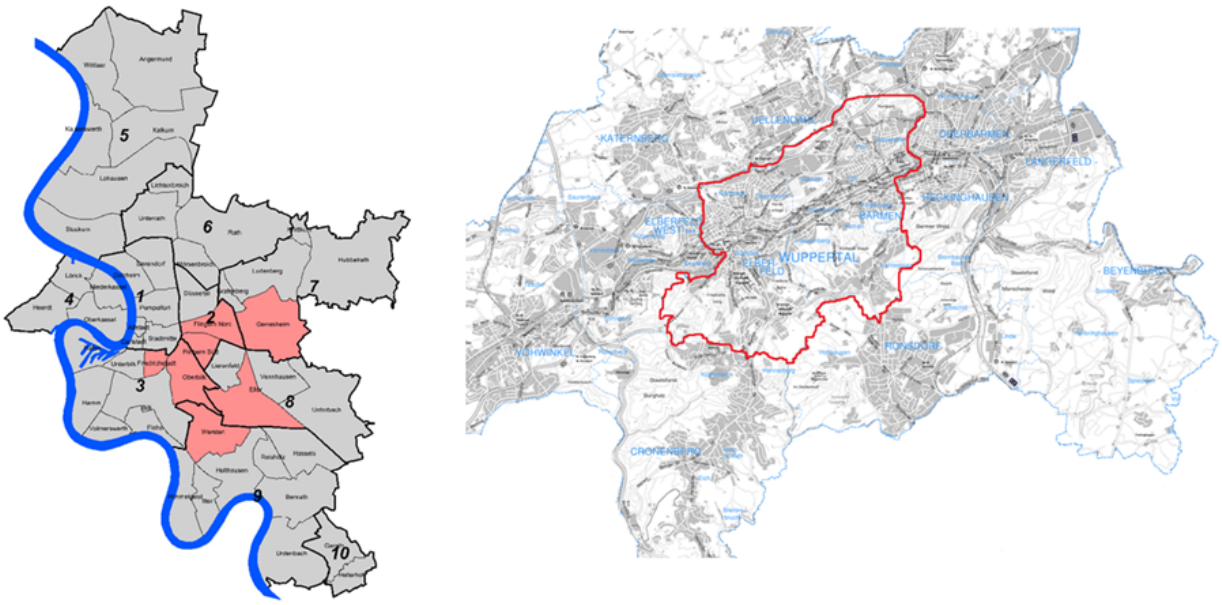
1. Is the intervention "10,000 Steps Ghent" adaptable and transferrable to the context of city districts in the state of North Rhine-Westphalia?
2. Is the intervention "10,000 Steps Duesseldorf" effective for the promotion of PA among residents of the districts involved?
   - Do individuals located in the city that the intervention is implemented in (Duesseldorf) engage in more PA compared with individuals located in the control city (Wuppertal) after 1 year? Does the absolute number of steps taken per week increase more for individuals residing in the intervention city than in the control city?
   - Does the proportion of those achieving the PA goal of 10,000 steps increase more in the intervention than in the control city after 1 year of potentially being able to participate in intervention activities?
   - To what extent can these differences be attributed to the adoption, implementation, and maintenance of the intervention in the intervention city compared with the control city?
3. What are the costs associated with the provision of the intervention? Does the intervention affect health care use and indirect costs? Is the intervention cost-effective in terms of additional costs per additional person who achieves the PA goal of 10,000 steps and additional costs per additional quality-adjusted life year (QALY) gained compared between the intervention and control cities after 1 year of potentially being able to participate in intervention activities?

Methods

Selection of Intervention and Control City Districts, Participants, and Procedures

The effectiveness of the community-based intervention for the promotion of PA is examined over the course of 1 year in a controlled intervention study. The PA behavior of individuals aged 25 to 75 years residing in the intervention districts of the city of Duesseldorf will be compared with that of individuals residing in the respective control districts of the city of Wuppertal at baseline and 1 year. Random samples were drawn based on data from the respective residents' registration offices. As the size of the cities in North Rhine-Westphalia did not permit an assessment of all residents living in both cities, as was done in the original study [14], adjacent city districts were selected that encompass a similar number of residents as the cities included in the original study. Publicly available information on the levels of socio-spatial deprivation of the districts of Duesseldorf and Wuppertal was used [28,29] during the selection process to ensure a composition of districts balanced by the proportions of residents living in them. The socio-spatial deprivation index is composed of indicators, such as welfare benefits, living space per person, and migrant population. In Duesseldorf, the index ranges from 1 (no deprivation) to 5 (high deprivation), and in Wuppertal, the index ranges from 1 (no deprivation) to 4 (high deprivation). Corresponding to the heterogeneous population of the original study, the Duesseldorf districts of Flingern Nord, Flingern Sued, Oberbilk, Friedrichstadt, Gerresheim, Eller, and Wersten and the Wuppertal districts of Elberfeld and Barmen were chosen. The selected areas and districts in the 2 cities are shown in Figure 1 [30].

Figure 1. Intervention and control city district areas (left, source: Jugendamt Landeshauptstadt Düsseldorf [Youth Welfare Office, State capital Duesseldorf]; right, source: Offene Daten Wuppertal [30]).



Sampling

On March 1, 2021, a random sample of 2500 residents (25-75 years) based on postal codes (500 individuals per age group: 25-35, 36-45, 46-55, 56-65, and 66-75 years) was drawn for the Duesseldorf districts of Flingern Nord, Flingern Sued, Oberbilk, Friedrichstadt, Gerresheim, Eller, and Wersten, and 2500 residents, using the same distribution, were sampled for the Wuppertal districts of Elberfeld and Barmen. Equal proportions of men and women were included. Thus, the overarching setting in this study is the respective city district in both cities, and the subordinate settings for the implementation of the complex intervention are the organizations located in these districts (eg, senior citizen associations, sports clubs, and companies), as well as the public spaces located in them (eg, parks and green spaces).

Recruitment

Recruitment for the study was conducted from mid-May to the end of December 2021. Individuals were informed about the study and invited to participate in it via mail. The study information, including information on data protection and the consent form (Multimedia Appendix 1), was provided in the mailed letters. Individuals interested in participating in the study were asked to return the signed consent form (and keep one for their records) and a form, including their telephone number, to the study team in the mail. Alternatively, they could contact the study team directly to make an appointment for the baseline interview and return the signed consent form after the completion of the telephone interview. However, in that case, verbal consent was provided by participants at the beginning of the telephone-based interview. In total, 3 invitation letters were sent to potential participants, and 2 reminder letters were sent 3 and 6 weeks after the first invitation letter. Once contact information was provided by a potential participant, up to 4 phone calls were made to reach the person and schedule an appointment for the baseline interview.

Owing to the COVID-19 pandemic, we expected the response rate to be extraordinarily low. To ensure that we reached the required sample sizes in both cities, a second random sample of another 4000 residents (2,000 in each city) was randomly drawn in both cities and with the same age and gender composition on July 29, 2021. During the second wave of recruitment, only 1 invitation and 1 reminder letter 4 weeks later were sent. Individuals were included in the study if they were (1) between the ages of 25 and 75 years, (2) able to understand German, and (3) residing in Duesseldorf or Wuppertal.

The baseline assessments started at the end of May 2021 and were completed at the end of March 2022. Baseline assessment entails a questionnaire completed by participants over the phone. Two study nurses and 4 student assistants underwent structured training to conduct the 1-hour telephone interviews. Data entry is done simultaneously to the interview over the secured web application, REDCap (Research Electronic Data Capture; Vanderbilt University). The respective REDCap study database is hosted at the Institute for Biometrics and Epidemiology at the German Diabetes Center Duesseldorf and is part of the regular Institute for Biometrics and Epidemiology at the German Diabetes Center IT environment with respect to data security and backups. After the interview, study participants are asked to track their PA over 7 consecutive days using the YAMAX EX210 pedometer, which records daily number of steps. In addition, they are asked to complete a wear-time diary to document the steps walked every day, the times the pedometer was worn, and the possible reasons for not wearing it. After 7 days, participants return the pedometer to the study team via mail, using a stamped return envelope provided by the study team. To validate the pedometer data, a subsample of approximately 30% of study participants receives an

accelerometer (ActiGraph wCT3X-BT; ActiGraph LLC) in addition to the pedometer, which they are asked to return in a stamped return envelope after 7 days of wear time. The intervention is being implemented in Duesseldorf for 1 year since April 2022, and follow-up assessments will be conducted, starting in May 2023. The same participants who participated in the baseline assessments will be contacted again via mail, invited to participate in the telephone-based interviews again, and asked to wear pedometers (and accelerometers) for 1 week afterward. To ensure confidentiality, all person-related data assessed in this study will be pseudonymized; that is, all study participants will be assigned an ID number. The roster with the names and ID numbers will be saved in a password-protected file on the server of the Institute of Medical Sociology. The data will be stored for 10 years after the completion of the trial and deleted afterward.

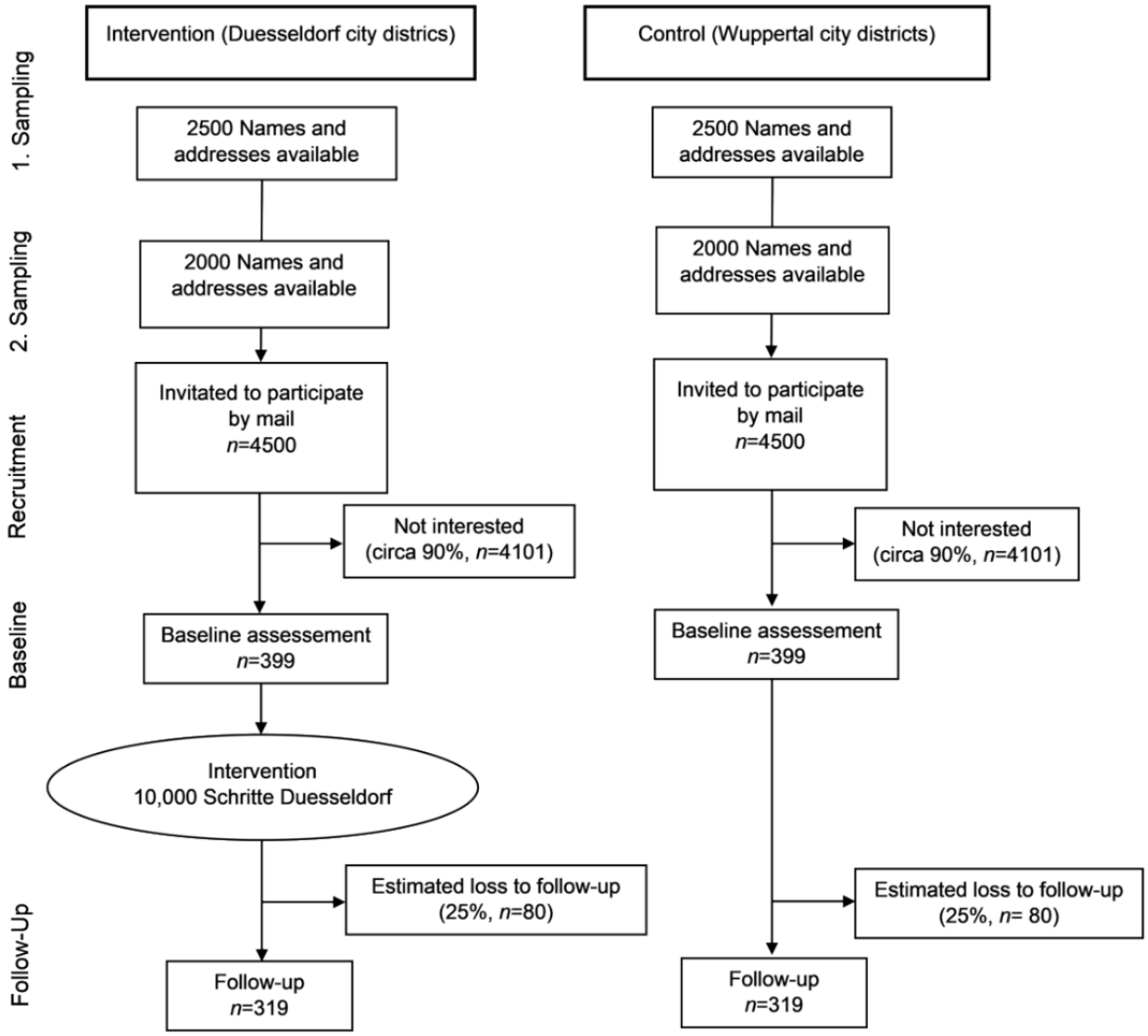
Ethics Approval

Ethics approval to conduct the study was obtained from the Ethics Committee of the Medical Faculty of the Heinrich Heine University Duesseldorf (reference number: 2021-1364; April 6, 2021). The study was registered in the German Clinical Trials Register on April 21, 2021 (trial number: DRKS00024873). All study participants are fully informed about the study and are requested to provide informed consent.

Sample Size Calculation

A number of 1000 steps were assumed as the minimal relevant effect. According to the previous study by De Cocker et al [14], the SD of the number of steps is ≤4500. This ensures a power of 80% for a 2-sided *t* test at the 5% level with a total of 638 patients (SAS, version 9.4, PROC POWER, TWOSAMPLEMEANS statement). A total of 798 participants were included in the study to compensate for an expected dropout rate of 25%. It should be considered that the power calculated here represents a lower limit because a noticeable gain in power is expected in the planned analysis owing to the adjustment for baseline characteristics of participants. Figure 2 shows the study design.

Figure 2. Study design.



Statistical Analyses

We will use the propensity score method for statistical analysis to allow for a nonrandomized design of the study. Specifically, the primary outcome will be estimated in a weighted 2-group comparison (intervention: yes vs no). For weighting, we will use matching weights [31] that are derived from a propensity score model for the intervention effect and an exhaustive list of covariates (Multimedia Appendix 2). The analysis will be blinded for the intervention effect and performed according to the intention-to-treat principle; missing values will be replaced via multiple imputation.

Measures and Outcomes

Sociodemographic characteristics of study participants, such as age, migration background, marital status, and socioeconomic status (including education, employment status, occupation, and income), as well as history of chronic disease and current diagnoses are assessed during the telephone interview.

Primary Outcome

The primary outcome is the number of steps assessed via pedometers. Participants are asked to track their steps using the YAMAX EX210 pedometer, which records the daily number of steps. They are also requested to complete a wear-time diary to document the steps walked every day, the times the pedometer is worn, and the possible reasons for not wearing it. PA is also assessed using the Global Physical Activity Questionnaire in the telephone-administered questionnaire [32]. It is one of the most frequently used questionnaires for measuring PA with high levels of reliability and validity reported when comparing it with other PA questionnaires (International Physical Activity Questionnaire—Short Form and European Health Interview Survey—Physical Activity Questionnaire) [33]. On the basis of the Global Physical Activity Questionnaire, the number of minutes spent on MVPA and different types of movement will be determined (eg, for transport, see Table 1). This questionnaire was chosen because it is also used in the National Cohort (NAKO) health study [34], a large German national cohort, allowing for a comparison of PA levels of our sample to a large population-based sample.

Furthermore, a subsample of our study participants also receives an accelerometer (wCT3X-BT) to track habitual PA. Participants are instructed to position the device at their nondominant wrist during the day to capture triaxial acceleration at a sample rate of 30 Hz. Data will be processed with ActiLife (version 6.13.4) software (ActiGraph LLC), using the algorithm by Choi et al [38] to derive valid wear times with at least 4 days of a minimum 8 hours (480 minutes) wear time. Within 10-second epochs, data are analyzed using cut-off points for MVPA, energy expenditure, and metabolic equivalent of tasks, according to Freedson et al [39].

Table 1. Outcomes assessed in the telephone-administered interviews (part 1).

Instrument or scale and outcome	Time of assessment
Socioeconomic characteristics	
NAKO[a] core interview [34]	
Date of birth	T_0[b]
Country of birth	T_0
Country of birth outside of Germany	T_0
Time since living in the territory of the Federal Republic of Germany or DDR	T_0
Nationality (German vs other)	T_0
Country of birth (father and mother)	T_0
Marital status	T_0
In a relationship	T_0
Living together with partner	T_0
Living district	T_0
Type of residence	T_0
Number of individuals living in the household	T_0
Number of individuals in the household >14 years	T_0
Highest education degree obtained	T_0
Types of educational qualifications	T_0
Other types of educational qualifications	T_0
Employment status (eg, full time or part time or unemployed)	T_0
Working hours per week	T_0
Previous employment status (full time or part time)	T_0
Occupation	T_0
Income level	T_0
Average net monthly income	T_0
NAKO "Corona-questionnaire" CO-1 question no. 19 [35]	
Changes at work due to the COVID-19 pandemic	T_0, T_1[c]
Self-generated item	
City that participant is working in	T_0
ALPHA[d] long version [36]	
Distance to work (km)	T_0
Züll [37]	
Type of occupational group	T_0
Self-employed or employed	T_0
Built environment and PA[e]	
ALPHA environmental questionnaire (long version) [36]	
Type of resident buildings in the immediate neighborhood	T_0
Pedestrian accessibility of stores in the immediate neighborhood	T_0
Infrastructure of footpaths and cycle tracks in the immediate neighborhood	T_0

Instrument or scale and outcome	Time of assessment
Quality of the living environment in the immediate neighborhood	T_0
Safety in the living environment in the immediate neighborhood	T_0
Attractiveness of the living environment in the immediate neighborhood	T_0
Connectivity of the living environment in the immediate neighborhood	T_0
Private equipment to support PA	T_0
Equipment in the work environment	T_0
PA	
GPAQ[f] [32]	
Intensive PA during paid and unpaid work	T_0, T_1
Days of intensive PA in a usual week at work	T_0, T_1
Time of intensive PA on such a day at work	T_0, T_1
Moderate PA at work	T_0, T_1
Days of moderate PA in a usual week at work	T_0, T_1
Time of moderate PA on such a day at work	T_0, T_1
Locomotion by foot or bicycle	T_0, T_1
Days in a usual week getting around from one place to another by foot or bicycle	T_0, T_1
Time invests to get from one place to another by foot or bike	T_0, T_1
Intensive PA during leisure time	T_0, T_1
Days of intensive PA in a usual week during leisure time	T_0, T_1
Time of intensive PA in a usual week during leisure time	T_0, T_1
Moderate PA during leisure time	T_0, T_1
Days of moderate PA in a usual week during leisure time	T_0, T_1
Time of moderate PA in a usual week during leisure time	T_0, T_1
Time of sedentary behavior on a usual day	T_0, T_1
Changes of PA in the past year in general	T_0, T_1
NAKO "Corona-Questionnaire" CO-1 question number 31 [35]	
Changes of PA caused by the COVID-19 pandemic	T_0, T_1

[a]NAKO: National Cohort Health Study.

[b]Baseline assessment.

[c]Follow-up assessment.

[d]ALPHA: Instruments for Assessing Levels of Physical Activity and Fitness

[e]PA: physical activity.

[f]GPAQ: Global Physical Activity Questionnaire

Secondary Outcomes

Secondary outcomes assessed at baseline and follow-up in the telephone-administered interview are described in detail in Table 2.

Briefly, at the individual level, height and weight, general self-rated health, and health behavior (smoking status, fruits and vegetables consumption, and alcohol use) are assessed. In addition, the determinants of PA are assessed (eg, social support). At the environmental level, perceptions of characteristics of the physical environment relevant for engaging in PA are assessed. To assess knowledge and awareness of intervention messages and activities spread and implemented in the intervention city districts, self-generated items are included in the follow-up questionnaire. Study participants are also asked about health care use (physician's visits, contacts with therapists, hospital stays, and rehabilitation) retrospectively for the previous 6 months and costs pertaining to devices bought to support engagement in PA or membership fees (eg, gym membership), as well as sick leave days.

Table 2. Outcomes assessed in the telephone-administered interviews (part 2).

Instrument or scale and outcome	Time of assessment
Determinants of PA[a]	
GEDA[b] [40], question no. 104 and 105 + 1 self-generated item	
Reasons to be or not to be physically active (including pandemic)	T_0[c], T_1[d]
GEDA [40], question no. 102	
Intention to increase PA in future	T_0, T_1
Sudeck et al [41]	
Movement-related self-efficacy	T_0, T_1
Self-generated items	
General knowledge of health benefits of PA, tracking of PA to date (use of devices; eg, pedometer, wearable, or smart watch)	T_0, T_1
Intention to be physically active [21]	
How would you like to be physically active more often in the future?	T_0, T_1
Modified version of questionnaire of Chernyak et al [42]	
Purchases of equipment to promote your fitness, health and well-being (past 6 months)	T_0, T_1
Health status	
SF-1[e] [43]	
How would you describe your health in general?	T_0, T_1
EQ-5D-5L [44]	
Perceived health (eg, mobility, pain or physical discomfort, or anxiety)	T_0, T_1
GEDA [45]	
Do you have a chronic illness or long-term health problem? (>6 months)	T_0
Present diseases or conditions in the past 12 months	T_0
Have you had high blood pressure or hypertension in the last 12 months?	T_0
Have you ever been diagnosed with high blood pressure by a physician?	T_0
Are you currently taking antihypertensive medications?	T_0
Have you had elevated blood lipids or elevated cholesterol in the past 12 months?	T_0
Have you ever been diagnosed with elevated blood lipids or elevated cholesterol by a physician?	T_0
Are you currently taking medication for elevated cholesterol?	T_0
Smoking habits	T_0, T_1
GEDA [45], modified	
How often do you eat fruits, vegetables and salad?	T_0, T_1
How many servings of fruits, vegetables and salad do you eat per day?	T_0, T_1
SOEP[f]-Core–2018, question no. 146 [46]	
What is your height in cm?	T_0, T_1
SOEP-Core–2018, question no. 147 [46]	
How many kilograms do you currently weight?	T_0, T_1
Alcohol Use Disorders Identification Test Short Version, translation from PROMOTE I [27,47]	
How often do you drink alcohol?	T_0, T_1
If you drink alcohol in a day, how many alcoholic beverages do you typically drink?	T_0, T_1

Instrument or scale and outcome	Time of assessment
Modified version of the questionnaire of Chernyak et al [42]	
Have you seen a physician in the last 6 months?	T_0, T_1
Which physicians have you seen in the last 6 months? (eg, general practitioner, gastroenterologist, diabetologist)	T_0, T_1
How many contacts you had in each of the last 6 months and how much time you spent in total on your outpatient?	T_0, T_1
Have you been to a therapist (eg, psychotherapist, physical therapist, speech therapist) for treatment in the last 6 months?	T_0, T_1
Which therapists have you seen in the last 6 months?	T_0, T_1
How many treatment sessions have you had in each of the last 6 months? And what is the total amount of time you spent on your treatment sessions?	T_0, T_1
Have you been hospitalized for inpatient treatment in the last 6 months?	T_0, T_1
Please indicate the reason and duration of stay for each hospitalization.	T_0, T_1
Have you been to rehabilitation in the last 6 months?	T_0, T_1
Indicate for each stay whether it was outpatient or inpatient rehabilitation. Please indicate the duration of your stay.	T_0, T_1
Please indicate how many days in total.	T_0, T_1
If your sick leave has been for more than 6 months, please indicate how many days you have been on sick leave.	T_0, T_1
Competences	
German translation of ICECAP-A[g] [48]	
Feeling safe and secure	T_0, T_1
Love, friendship, and support	T_0, T_1
Be independent	T_0, T_1
Performance and progress	T_0, T_1
Pleasure and enjoyment	T_0, T_1
Movement-related networks and social networks	
Jackson et al [49]; Fuchs [50], adapted	
Perceived social support for PA by family members and friends	T_0, T_1
Perception and use of the intervention[h]	
Self-generated items	
Awareness of the intervention, use of various intervention components	T_1

[a]PA: physical activity.

[b]GEDA: Gesundheit in Deutschland aktuell.

[c]Baseline assessment.

[d]Follow-up assessment.

[e]SF-1: Short Form-1.

[f]SOEP: Sozio-oekonomisches Panel.

[g]ICECAP-A: The ICEpop CAPability measure for adults.

[h]Only assessed in the intervention group.

Intervention

Participatory Design

The start of the study was preceded by a 6-month participatory phase to recruit relevant stakeholders from the city of Duesseldorf to a stakeholder advisory board supporting the research team in the development and implementation of the intervention. Relevant stakeholders include representatives of the involved local communities, the public health service, the city of Duesseldorf's administrative offices for sports and social services, 2 statutory health insurances, and the city's Chamber of Industry and Commerce (*Industrie und Handelskammer*), as well as several companies, the physician's chamber, and the city's soccer club. These stakeholders were invited to participate in the board during the first 2 months of the participatory development phase. In months 3 to 6 of this phase, monthly

meetings were held to adapt the Ghent intervention to the Duesseldorf context and develop a joint strategy for implementing the intervention. During these meetings, ideas concerning intervention activities and the steps necessary for implementation were brainstormed and continuously prioritized. The meetings will be continued during the implementation phase of the intervention.

Intervention Components

The complex intervention "10,000 Steps Düsseldorf" is a universal prevention approach aimed at motivating residents of the intervention districts of Duesseldorf to be more physically active in everyday life. The intervention components are described in further detail in the subsequent sections. In addition, Table 3 compares intervention content of "10,000 Steps Duesseldorf" to the preceding interventions in Ghent and Rockhampton.

Table 3. Socioecological intervention components and dissemination strategies of "10,000 Steps" studies (adapted based on Van Acker et al [51]).

	10,000 Steps Rockhampton (2-year project)	10,000 Steps Ghent (1-year pilot)	10,000 steps in Flanders	10,000 Steps Duesseldorf
Intrapersonal	• Sale (GP[a] and health services) and loan (libraries and video shops) of pedometers • Website of "10,000 Steps Rockhampton"	• Sale (local town shop, and health services) and loan (sport service) of pedometers • Website of "10,000 Steps Ghent"	• Sale and loan of pedometers in every municipality (local public services) • Website updated from "10,000 Steps Ghent"	• Website of 10,000 steps in Duesseldorf • Provide recommendations for step counters and PA[b] trackers on the website of "10,000 Steps Düsseldorf"
Interpersonal	• Promotion of PA by health professionals and print media	• Promotion of PA and distribution of folders through GPs, dietitians, physical therapists, and schools; posters in public places	• Promotion of PA and distribution of folders and posters in public places • Personalized contact with citizens (eg, personalized letter, mail, or phone)	• Promotion of PA via step-count competitions with family and friends
Organizational	• Community events and specific projects for GPs, for health services involvement, and for workplaces	• Community events and specific projects for workplaces and for groups of older people	• Community events and projects for the entire population and all domains of active living (PA for transport, at work, in the household, and during leisure time)	• Community events and specific projects for workplaces (step-count competitions) and for groups of older people
Community	• Local mass media campaign • 10,000 Steps a Day—Every Step Counts • Environmental: street signs, distribution of maps, and promotion of dog walking	• Local media campaign • 10,000 Steps a Day—Every Step Counts, 30 minutes MVPA[c] guideline • Environmental: street signs, walking circuits and billboards	• Local mass media campaign in every municipality • 10,000 Steps a Day—Every Step Counts, 30 minutes MVPA guideline • Environmental: street signs and walking circuits	• Local mass media campaign • 10,000 Steps per Day—Every Step Counts • Environmental: street signs and distribution of maps
Policy	• Partnerships between local government and key members of community organizations, some with high-level experience in PA promotion • Sale and loan of pedometers	• Partnerships between the local city and provincial government, health insurance companies, and the local health promotion service • Sale and loan of pedometers	• Partnerships between the adopting organization and a minimum of 1 (other) local government service or 2 professional organizations • Sale and loan of pedometers	• Partnerships between local government and key members of community and professional organizations, health insurance companies, and commercial organizations targeting PA (eg, local soccer clubs)
Strategies for dissemination among potential adopters	• Local: recruitment of community partners by researchers (micro-grants) to form a local PA task force and GP training	• Local: recruitment of community partners by researchers to form a local steering committee	• Regional: website, mailing of the project manual and pilot study results, group meetings, displays at conferences, and e-articles	• Local: recruitment of community partners by researchers to form a local steering committee; a website and e-mailing of invitations to participate, including a checklist for intervention implementation

[a]GP: general practitioner.

[b]PA: physical activity.

[c]MVPA: moderate to vigorous physical activity.

Intrapersonal Level: "10,000 Steps Duesseldorf" Website

The website was jointly developed with a marketing company and is based on the content of the website of the Flemish Institute of Healthy Living and Ghent University [52]. The content of the website is based on several behavior change techniques (eg, goal setting [behavior], discrepancy between current behavior and goal standard, self-monitoring of behavior, and social comparison [53]). It contains the WHO recommendations for PA and information on why and how to increase the personal daily step count, including health benefits. The target groups are individuals, groups (circles of friends and acquaintances), and organizations (eg, companies). In line with the main intervention message "Every Step Counts," tips and information are provided on how to integrate more steps into everyday life. There are also recommendations for steps counters and PA trackers and a calendar indicating current events and offers regarding PA in the city of Duesseldorf. Visitors can

create a personal profile to monitor steps, receive weekly and monthly overviews of steps, upload photos, convert other activities to steps (eg, bicycling or swimming), compare and exchange ideas with other intervention participants, and participate in step-count competitions. Information on the ongoing study examining the effects of the intervention is also included, along with references to previous projects in Ghent and Rockhampton.

Interpersonal Level: Promotion of PA in Groups

In step-count competitions with family and friends organized via the website, individuals are encouraged to monitor their steps, set goals, and motivate each other to engage in PA. The step-count competitions will take place as events in the entire city or in selected city districts. Step-count competitions will also take place in companies.

Organizational Level: Specific Projects for the Workplace and for Groups of Older People

Step-count competitions organized via the website will be advertised and implemented in companies and other organizations located in the intervention districts. Members of the stakeholder advisory board will help publicize the program and its website via email lists of companies, general practitioners, senior citizen clubs, sports clubs, and health insurance offices and by using their social media channels. In addition, print materials describing the aim and content of the intervention (brochures, flyers, and stickers), which were developed based on the print materials of 10,000 Stappen will be made available to organizations.

Community Level: Community Events, Local Mass Media Campaign, Environmental Street Signs, and Walking Circuits

A range of community events focusing on PA promotion are foreseen, such as the ascent of the Duesseldorf television tower (*Skyrun*), a family event in the local soccer stadium with representatives of the soccer team, and city rallies with different local themes coming from arts, culture, and history. In addition, the project will be linked to existing events, such as events organized by Duesseldorf's administrative office for sports, city marathons, and events for health promotion organized by other entities. These events will be publicized via press releases and via the website's social media channels and the members of the stakeholder advisory boards' social media channels. The main intervention message, "Every Step Counts," will be disseminated via various media channels and in public places. The aim of the media campaign is to encourage participation, as well as linking up with existing events in Duesseldorf. Flyers, as well as stickers and brochures, will be provided at the events.

In addition, for each intervention district, routes have been developed that support residents in reaching 10,000 steps per day. There is a range of 30- to 60-minute routes that can be easily integrated into everyday life and reflect the guiding principle of the project. In this context, the project's own "Komoot" account (Komoot is an app to plan routes and socially network regarding outdoor activities) was created, on which suitable tours will be shared, which can also be shared on the website. The tours fulfill various criteria (eg, good lighting, security, accessibility, availability of seating and public toilets, and general attractiveness). Signage with routes, including information on the number of steps, and QR codes to the website will be posted in parks and public spaces of the intervention districts.

Process Evaluation

The aim of the process evaluation is to document the frequency and intensity of the implemented intervention activities at every level of the complex intervention over the course of 1 year. This ensures intervention fidelity, meaning that it will be possible to assess whether the implementation of the intervention in Duesseldorf, Germany, was comparable with the implementation of the original intervention in Ghent. According to the RE-AIM framework [54], reach (the extent to which the program reaches the intended target group), effectiveness, adoption, implementation, and maintenance (of individual behavior change of the target group as well as long-term decision-making behavior of relevant stakeholders to consolidate intervention activities) will be assessed. A similar approach will be followed as developed by Van Acker et al [51].

For this study, the five components of the framework will be determined based on various data sources: (1) the commercial register of companies located in the intervention districts or the register of the Chamber of Commerce and Industry, (2) the individual-level data assessed in the telephone-administered interviews, and (3) a web-based questionnaire that heads of participating organizations (eg, companies) will be invited to participate in. The web-based questionnaire includes four thematic item blocks regarding (1) the characteristics of the respective organization (eg, company size) and knowledge of the intervention, (2) the adoption of the intervention and reasons for or against adoption, (3) the implementation of the intervention (eg, of the different intervention components, frequency and duration, and resources needed to implement the intervention or raise awareness), and (4) long-term intervention maintenance (reasons for or against it). Examples of the items in the web-based survey are shown in Textbox 1.

To estimate reach, first, the number of organizations potentially participating in the program in each intervention district will be determined based on the commercial register or by the Chamber of Commerce and Industry. Second, the number of organizations participating in the program will be assessed and surveyed using the web-based questionnaire. Furthermore, the proportion of individuals who were aware of intervention activities will be calculated, and to determine representativeness, age, gender, level of education, and occupation of those aware of the intervention will be compared with those unaware of the intervention. Effectiveness will be determined by comparing the 4 domains of active living (PA for transport, to work, in the household, and during leisure time activities) among individuals with and without awareness of the intervention. Adoption will be determined by estimating the proportion and representativeness of organizations implementing the intervention (compared with those not implementing the intervention). The implementation of the different intervention components (website, print-based materials, and initiation of partnerships) will be assessed, and an implementation score

ranging from 0 to 100 will be calculated (see the study by Van Acker et al [51] for more details regarding the calculation of the score). To estimate maintenance, the proportion of organizations that voiced the intention to maintain the intervention will be determined.

Textbox 1. Example items of the web-based questionnaire used in the process evaluation.

Thematic block and examples of items

1. Characteristics of the respective organization and knowledge of the intervention
   - In which organization do you work?
   - How many permanent employees does your organization have?
2. Adoption of the intervention and reasons for or against adoption
   - Did your organization participate in 10,000 Steps Duesseldorf?
   - What contributed most to the decision to carry out 10,000 Steps Duesseldorf?
   - What are the main reasons why 10,000 Steps Duesseldorf was not implemented?
3. Implementation of the intervention
   - How many employees worked on the implementation of 10.000 Steps Düsseldorf?
   - What was or is the total investment, excluding staff costs, for your organization to implement 10,000 Steps Duesseldorf?
   - Did you distribute the program materials (stickers, brochures, flyers) of 10,000 Steps Duesseldorf?
   - Which media channels did you use and at what cost?
4. Long-term maintenance of the intervention
   - Does your organization intend to plan further intervention activities in the future following the past or current 10,000 Steps Duesseldorf activities?
   - Why are no 10,000 steps Duesseldorf program activities planned for the future?

Health Economic Evaluation

The health economic evaluation will include a cost-effectiveness analysis (CEA) and a cost-utility analysis from a societal perspective. An incremental cost-efficacy ratio (ICER; additional costs per additional person walking 10,000 steps/day) and an incremental cost-utility ratio (ICUR; additional cost for an additional QALY gained) will be determined. The outcome of the CEA is based on the primary outcome of the intervention and will be taken from the step counter measurement. QALYs will be calculated based on the EQ-5D-5L [44], which is a widely used standardized instrument to assess health-related quality of life. The EQ-5D-5L is evaluated using a German tariff to obtain preference weights [55]. As the intervention might influence people beyond health, we will also consider capability well-being using the ICEpop CAPability measure for adults (ICECAP-A) [48]. We will use a UK scoring tariff because a German tariff does not exist yet [56] and compare utilities based on capabilities with those based on QALYs.

The costs considered in the health economic evaluation comprise costs related to the development and provision of the intervention (eg, print-based materials, website, and time associated with the development of the intervention as opportunity costs), health care use (physician's visits, contact with therapists, hospital stays, and rehabilitation), and costs associated with PA behavior (devices to support PA, membership fees [eg, gym membership], disability to work, and patient time). Productivity loss due to disability to work is calculated based on the human capital approach [57]. In a sensitivity analysis, patient time associated with PA, evaluated via opportunity costs, will also be examined. A discounting of costs and outcomes is not planned because of the short study duration.

The analysis will be performed according to the intention-to-treat principle. In the base case analysis, missing values will be imputed via multiple imputation. To make the random samples from the intervention and control region comparable, propensity score matching in the form of a weighted regression model will be applied after the imputation and for each imputed data set as suggested by Al-Janabi et al [58]. Covariates used for the matching will be the number of steps taken at baseline, age, gender, level of education, and household income.

Mean incremental costs and the mean incremental outcome of the CEA will be estimated by a using a Generalized Linear Model with gamma distribution and log link function. To estimate the mean incremental outcome of the CEA (an additional person who walks 10,000 steps/day), a Generalized Linear Model with binomial distribution and logit link function will be estimated. Bootstrap procedures will be used to calculate 95% significance intervals for the ICER and ICUR [59,60]. To investigate uncertainty surrounding the ICER and ICUR, cost-effectiveness and cost-utility planes will be generated [61,62].

Results

Funding for this study was obtained in March 2020. Recruitment for this study and baseline data collection were conducted from May 2021 to March 2022 (as of March 2022, 626 participants were enrolled in the study). The intervention is being implemented in Duesseldorf for 1 year from April 2022 onward, and follow-up assessments will be conducted, starting in May 2023 (until September 2023). Data analysis will be performed in fall 2023, and the results will be published in spring 2024.

Discussion

Anticipated Principal Findings

To the best of our knowledge, this is the first study in Germany aimed at replicating the effects of a complex intervention for PA promotion previously shown to be effective in another European country. The study findings will contribute to the growing body of evidence in Germany concerning the role of complex community-based interventions for the promotion of PA in the general population [19-27]. We anticipate to obtain results similar to those reported in the original study, where adults exposed to a complex PA intervention for 1 year displayed a greater increase in daily step count (ie, average of daily steps walked increased by 896 in intervention vs no increase in the comparison city) and were more likely to reach the WHO recommendation for PA than controls (ie, 8% increase in the number of individuals reaching the recommended 10,000 steps) [14]. With regard to the expected results of the process evaluation, we foresee that the processes involved in the implementation of the various intervention components may be somewhat different, as the organizational structures of administrative offices and community organizations in Germany may operate differently compared with Belgian organizations. However, by using a similar approach to monitoring processes, we expect to be able to compare our results with those obtained in the Ghent study. Furthermore, similar to the health economic evaluation of the original intervention indicating that the intervention was cost-saving [63], we expect "10,000 Steps Duesseldorf" to be cost-effective. Other previous health economic evaluations of population-level, community-based interventions addressing PA also demonstrated cost-effectiveness [64]. Finally, previous research suggests that community-based interventions involving local stakeholders in particular may yield intervention effects after the primary evaluation is completed [13,15,16]. Our study was preceded by a 6-month participatory planning phase involving key stakeholders of PA promotion in the city of Duesseldorf. Therefore, it is conceivable that the effects may become visible after the completion of the 1-year follow-up in our study.

Comparison With Prior Work

As outlined earlier, the primary focus is on the comparison with the Ghent- and Rockhampton-based studies. Furthermore, we expect that the recommendation and use of step counters will be associated with a similar increase in daily steps walked, as was previously reported in several reviews and meta-analyses synthesizing the results of studies examining the effects of population-based PA interventions [11,13]. The analysis of the accelerometer data of the subsample in our study will allow us to analyze weekly minutes spent on MVPA and compare the results to those reported by Wahlich et al [13] in their review and meta-analysis.

Strengths and Limitations

A major strength of this study is the use of an innovative methodological approach for examining the effects of a complex community-based PA intervention in Germany and the ability to compare the results obtained in this study to those reported in 2 other countries in 2 continents. To our knowledge, this is the first study to examine the effect of a multistrategy population-level intervention on PA behaviors targeting individuals aged ≥18 years, which was developed based on a participatory approach. Another strength is the use of objective measurements in a subsample of the study, allowing for the validation of the questionnaire data collected in the telephone-based interviews. A limitation is that, unlike in the original study, 2 entire cities could not be compared in terms of PA behavior of participants living in them. However, by balancing the city districts of both cities included in our study using indicators of socio-spatial deprivation, we hope to have obtained a similar sociodemographic composition of our study participants. Another limitation is the ongoing COVID-19 pandemic, which complicated the recruitment of study participants. Adjustments in the number of potential study participants contacted and invited to participate were necessary to offset the difficulties in enrolling participants to the study. Finally, in our study, a trial-based health economic evaluation is conducted that does not include modeling of long-term effects and costs. Nevertheless, the health economic evaluation will provide detailed information to decision makers regarding short-term cost-effectiveness of the intervention.

Future Directions

Should this study reveal positive effects on PA in the intervention compared with the control city districts, conducting a 4-year follow-up to assess the long-term effects of the intervention on PA and quality of life, similar to Cocker et al [15], may be useful to demonstrate long-term effects. Furthermore, comparing the results of the 3 studies conducted in Rockhampton, Ghent, and Duesseldorf may help devise recommendations for adaptation and implementation in other European cities. In Germany, a rollout of the intervention in other cities (possibly starting with the control city, Wuppertal) could be a next step after the completion of the primary evaluation. A plan for scale up or dissemination will be developed at the end of the project. In the original Ghent-based study, the intervention was rolled out in all of Flanders and evaluated based on the RE-AIM framework [14]. A similar approach could be taken after completion of this study (eg, in the entire state of North Rhine-Westphalia or in an additional German state). Following the original study by Dubuy et al [18], combined baseline data from Duesseldorf and Wuppertal from this study could serve as a historical control group. Finally, future research may also include health economic modeling techniques that could shed further light on the long-term effects of intervention participation on cost-effectiveness of this

multistrategy approach for PA promotion at the community level.

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Data Availability

After the completion of the study, the data can be shared with other researchers upon request but only in research collaborations with the researchers of this study. The intervention content and materials will be further disseminated via the organizations and members of the stakeholder advisory board. Trial results will be published in joint press releases and social media posts of the stakeholders, which can also be made available on the intervention website. Furthermore, the results will be published in scientific articles and presented to the public health community at scientific conferences.

Authors' Contributions

PMMF, LG, ES, JT, and CRP drafted the manuscript. PMMF, CRP, LG, ES, SW, MV, AL, AI, OK, and SW contributed substantially to the conception and design of the study. All authors read, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent materials.
[PDF File (Adobe PDF File), 190 KB - resprot_v11i9e39175_app1.pdf]

Multimedia Appendix 2
List of covariates in the propensity score model.
[PDF File (Adobe PDF File), 12 KB - resprot_v11i9e39175_app2.pdf]

Multimedia Appendix 3
Review Proposals.
[PDF File (Adobe PDF File), 153 KB - resprot_v11i9e39175_app3.pdf]

Multimedia Appendix 4
Answers to Reviewers.
[PDF File (Adobe PDF File), 70 KB - resprot_v11i9e39175_app4.pdf]

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Abbreviations

AEQUIPA: Physical Activity and Health Equity: Primary Prevention for Healthy Ageing
CEA: cost-effectiveness analysis
HLCA : Health Literacy in Childhood and Adolescence
ICECAP-A: The ICEpop CAPability measure for adults
ICER: incremental cost-efficacy ratio
ICUR: incremental cost-utility ratio
MVPA: moderate to vigorous physical activity
NAKO health study: National Cohort health study
PA: physical activity
PROMOTE:
QALY: quality-adjusted life year
REDCap: Research Electronic Data Capture
WHO: World Health Organization

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Protocol

Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic pain and access to care are identified as critical needs of the Veterans Health Administration. Music imagery and music listening interventions have shown promise as effective nonpharmacological options for pain management. However, most studies have focused on acute pain, passive music experiences, and in-person delivery.

Objective: In this study, we aimed to examine the feasibility and acceptability of 2 music interventions delivered through telehealth for chronic musculoskeletal pain, trial design, and theoretical model before conducting a fully powered efficacy or comparative effectiveness trial.

Methods: FAMILIA (Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia) is a 3-arm, parallel group, pilot trial. A total of 60 veterans will be randomized to one of the three conditions: music imagery, music listening, or usual care. Aim 1 is to test the feasibility and acceptability of a multicomponent, interactive music imagery intervention (8-weekly, individual sessions) and a single-component, minimally interactive music learning intervention (independent music listening). Feasibility metrics related to recruitment, retention, engagement, and completion of the treatment protocol and questionnaires will be assessed. Up to 20 qualitative interviews will be conducted to assess veteran experiences with both interventions, including perceived benefits, acceptability, barriers, and facilitators. Interview transcripts will be coded and analyzed for emergent themes. Aim 2 is to explore the effects of music imagery and music listening versus usual care on pain and associated patient-centered outcomes. These outcomes and potential mediators will be explored through changes from baseline to follow-up assessments at 1, 3, and 4 months. Descriptive statistics will be used to describe outcomes; this pilot study is not powered to detect differences in outcomes.

Results: Recruitment for FAMILIA began in March 2022, and as of July 2022, 16 participants have been enrolled. We anticipate that enrollment will be completed by May 2023. We expect that music imagery and music listening will prove acceptable to veterans and that feasibility benchmarks will be reached. We hypothesize that music imagery and music listening will be more effective than usual care on pain and related outcomes.

Conclusions: FAMILIA addresses four limitations in music intervention research for chronic pain: limited studies in veterans, evaluation of a multicomponent music intervention, methodological rigor, and internet-based delivery. Findings from FAMILIA will inform a fully powered trial to identify putative mechanisms and test efficacy.

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KEYWORDS

chronic pain; music therapy; veterans; clinical trial; music imagery; pilot study; feasibility; acceptability; mobile phone

Introduction

Chronic Pain

Chronic pain, a persistent problem for United States veterans, has a reported prevalence as high as 65.5% in the veteran population and is associated with limitations in mobility and daily activities, dependence on opioids, anxiety and depression, and poor perceived health [1,2]. Chronic pain is often inadequately treated with analgesics alone and results in substantial disability, reduced health-related quality of life, and increased health care use and costs. Musculoskeletal pain accounts for more than half of all patients with pain disorders presenting for clinical care and analgesic treatment is insufficient for many patients [3,4]. To improve pain-related outcomes, the Department of Veterans Affairs (VA) recommends an integrative approach to pain management, including nonpharmacological interventions [5,6].

Music Therapy and Pain

Music therapy interventions target biopsychosocial outcomes and show promise as nonpharmacological options for pain. Music therapists use active (music making) and receptive (music listening) interventions to support pain management; however, much of the music and chronic illness literature comprises studies that use receptive interventions [7,8]. Studies of music listening interventions have demonstrated statistically significant reductions in self-reported pain, emotional distress, and opioid use, but the findings are inconsistent and although there are a few studies that address patients with chronic pain, the focus has been primarily on acute pain [9-13]. A majority of these studies evaluated recorded music listening programs, with inconsistent findings likely because of an absence of theoretical frameworks to guide music selection and tailored delivery, and educational components to encourage independent use of music. Music listening interventions often involve minimal interaction with a music therapist, and are primarily designed to be patient self-directed, empowering patients to use music whenever needed. However, some patients with complex pain and psychological comorbidities may need a more intensive and interactive music therapy intervention that includes ongoing support, symptom monitoring, and additional treatment components, such as imagery and verbal processing, to potentially enhance the therapeutic effects of music listening.

Compared with recorded listening programs, therapist-led music therapy interventions involve more interactive approaches to music listening that provide education about the therapeutic potential of music and often integrate additional treatment components (eg, lyric discussion, drawing or journaling) to address additional biopsychosocial factors that contribute to chronic pain [14,15]. Music imagery, a receptive music therapy intervention that combines music listening, imagery, and verbal processing, has been used to address a variety of patient needs (eg, symptoms related to posttraumatic stress disorder [PTSD], cancer, mood disorders, and chronic pain [16-19]). In pilot studies with nonpain populations (eg, PTSD, health care providers), participants found that music imagery enhanced their coping skills and ability to self-regulate [16,17]. Both music listening and music imagery have shown benefits for patients with fibromyalgia and other chronic pain illnesses, including improved well-being and decreased pain, anxiety, and depression [20-22]. Taken as a whole, the music therapy literature suggests that music listening and music imagery may improve pain outcomes, but gaps in the literature include inadequate evaluations among patients with chronic pain, theoretically grounded interventions, and lack of methodological rigor.

Telehealth Delivery

Although VA recommends using nonpharmacological interventions for chronic pain, there are significant barriers that limit access to creative arts interventions, including music therapy (eg, rural and homebound veterans [23]). Virtual delivery of health care can improve access, especially for the older adults, the mobility-impaired, and those living in rural areas or those with transportation barriers [24,25]. Case studies of virtually delivered music therapy have described veterans' endorsement of telehealth sessions and patient-reported benefits [26]. Although these studies provide compelling preliminary data, more research is needed to develop and test specific music interventions for chronic pain that can be delivered through telehealth. In this context, we will evaluate 2 music interventions (music listening and music imagery) for veterans with chronic musculoskeletal pain.

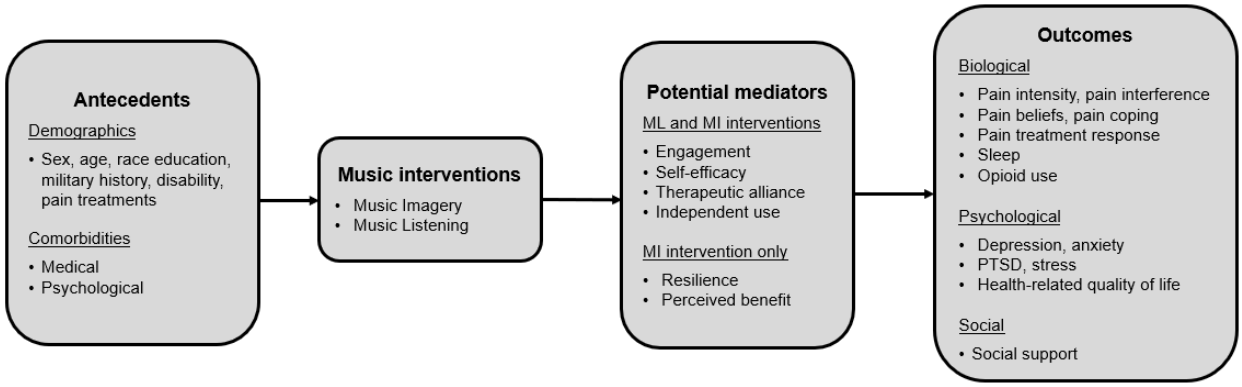
Study Innovation

The FAMILIA (Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia) study addresses four

limitations in music intervention research for chronic pain: few studies in veterans, evaluation of multicomponent music interventions, methodological rigor, and virtual delivery. Most previous studies described a passive, one-session, single-component music listening experience for patients with acute pain [9-13]. In contrast, the FAMILIA study will evaluate 2 music interventions in veterans. Compared with music listening, less is known about multicomponent music interventions, which we hypothesize are more robust in reducing pain owing to greater treatment intensity and more frequent interactions with a music therapist. The FAMILIA study will assess outcomes (feasibility, acceptability, pain, and associated outcomes) of a single-component, minimally interactive intervention (music listening) and a multicomponent, interactive intervention (music imagery).

Systematic reviews of music interventions for pain cite a lack of methodological rigor because of poorly described interventions, a lack of theoretical foundation, and no reporting of adverse events [27,28]. The FAMILIA study will address these methodological concerns in several ways. First, we will adhere to reporting guidelines for music-based interventions developed by Robb et al [29]. Second, we will use a theoretically based conceptual framework (Figure 1) to explore the hypothesized mechanism of action and outcomes. Third, we will systematically monitor for specific potential adverse events in both interventions.

Figure 1. Study conceptual framework. MI: music imagery; ML: music listening; PTSD: posttraumatic stress disorder.



FAMILIA addresses important knowledge gaps regarding virtual delivery of music therapy interventions. The COVID-19 pandemic has rapidly accelerated the widespread use of telehealth services for multiple chronic conditions, including chronic pain, but there are few published studies to guide virtual delivery of music therapy. We recently conducted the first enterprise-wide survey examining current practices in telehealth delivery by VA creative arts therapists. Initial results indicated that 76% of creative arts therapists have delivered virtual sessions, with 74% delivering >50 sessions in the past year [30]. Telehealth provides greater access, convenience, continuity of care, and support for veterans [31,32]. Early adopters of telehealth music therapy have provided general instructive examples, but there is a need for rigorous research of music interventions delivered virtually to determine their feasibility, acceptability, and efficacy [23,26,33]. We expect that our study will inform evidence-based practice and help expand access to music interventions for chronic pain.

Rationale and Specific Aims

The objective of this randomized controlled trial (RCT) is to examine feasibility and acceptability of the interventions, trial design, and theoretical model before conducting a fully powered efficacy or comparative effectiveness trial. Findings from FAMILIA will be used to refine the interventions and theoretical model, allowing for a comprehensive analysis of proposed mediators and outcomes in a subsequent trial. The 2 specific aims and the related key questions are shown in Textbox 1.

Textbox 1. Study aims and key questions.

Aims and Questions

Study aim 1: test the feasibility and acceptability of a multicomponent, interactive music imagery intervention and a single-component, minimally interactive music listening intervention.

- What percentage of veterans consent to study participation, attend intervention sessions, and complete the treatment protocol and scheduled outcome assessments?
- What are veteran experiences with both interventions?
- What aspects of the interventions do veterans perceive to be most or least helpful and most or least liked?
- What are barriers and facilitators to study participation?
- How did the music interventions compare to other chronic pain treatments already tried?

Study aim 2: explore the effects of both music interventions (music imagery and music listening) vs usual care on pain and associated patient-centered outcomes.

- What are the changes from baseline to follow-up assessments (1, 3, and 4 months) on pain and associated patient-centered outcomes?
- What are the changes in proximal and distal mediators, and do they vary based on group assignment?
- What proportion of veterans achieve a clinically meaningful change in pain intensity and pain interference?

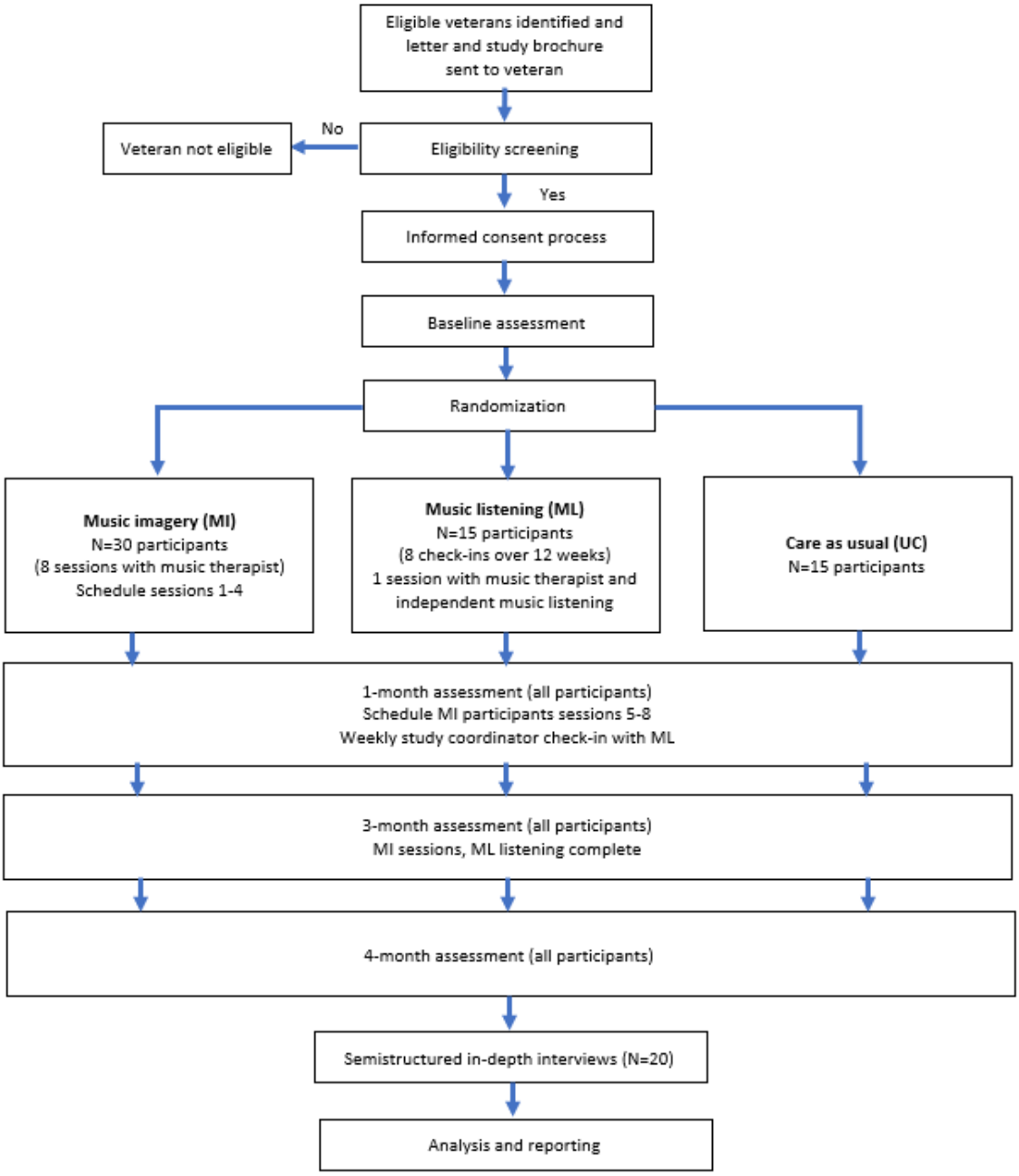
Methods

Study Design

The FAMILIA study is a 3-arm, parallel group, RCT, as shown in Figure 2. After providing informed consent and completing their baseline assessment, participants will be randomized in a 2:1:1 allocation ratio to 1 of 3 groups. Twice as many participants will be randomized to the music imagery group than other groups because a key goal of this pilot study is to gain experience with and learn about patients' perceptions of a multicomponent, interactive music therapy intervention. The goal sample size is 60 participants, with approximately 30 participants in the music imagery arm, 15 participants in the music listening arm, and 15 participants in the usual care arm. A sample size of 15 to 20 per group is sufficient to assess the feasibility and acceptability in pilot trials [34].

Randomization will be stratified according to biological sex (male vs female). Within strata, randomization with block sizes of 9 will be executed to ensure a balance of key baseline characteristics (eg, baseline pain intensity).

Figure 2. Flowchart of study design.



Sample Size and Randomization

Recruitment

The study population will include veterans receiving care through the Richard L Roudebush VA Medical Center, Indianapolis, Indiana, United States. Inclusion criteria are veterans with chronic musculoskeletal pain of at least moderate severity (graded by ≥5 on a 0-10 scale); access to a PC, tablet, or smartphone; and ability to pass a technology screening assessment. Veterans with serious or unstable medical or psychiatric illness, housing insecurity that would prevent study participation, or suicidal ideation with current intent are excluded from participation. Veterans with hearing or cognitive impairment are also excluded because of possible interference with music listening or abstract thinking needed for music imagery work.

Veterans will be recruited from primary and specialty care clinics. Study enrollment and intervention activities will primarily be delivered virtually through Microsoft Teams, which is a VA-approved audio and video platform. Participants will be provided the options of reviewing informed consent, completing their baseline assessment, and attending their initial music imagery or music listening session in person to build rapport and identify any technology concerns. Participation and refusal rates will be tracked throughout enrollment and reported in aggregate by study group.

Participant Recruitment Strategies

Recruitment strategies mirror those that have been successful in multiple previous pain trials [35-38]. Primary care physicians will be informed of study details and asked to refer patients they feel could potentially participate in the study. Potential participants will be identified by querying the VA's electronic medical record system to create a master list of veterans with the International Classification of Diseases 9th and 10th editions (ICD 9/10) codes for chronic musculoskeletal pain (ie, low back pain, neck pain or cervicalgia, fibromyalgia, and osteoarthritis). An invitation letter will be mailed to qualifying veterans to describe the study. Potential participants will be contacted by phone after the letter is mailed to assess eligibility and determine their interest in participating. Clinical staff may refer veterans who have not received a letter to the research team, and self-referral is possible by patients responding to a study brochure or advertisement displayed in primary care, orthopedic, rheumatology, pain, and rehabilitation clinics. The research team will determine eligibility by applying the inclusion and exclusion criteria to potential participants during an eligibility evaluation.

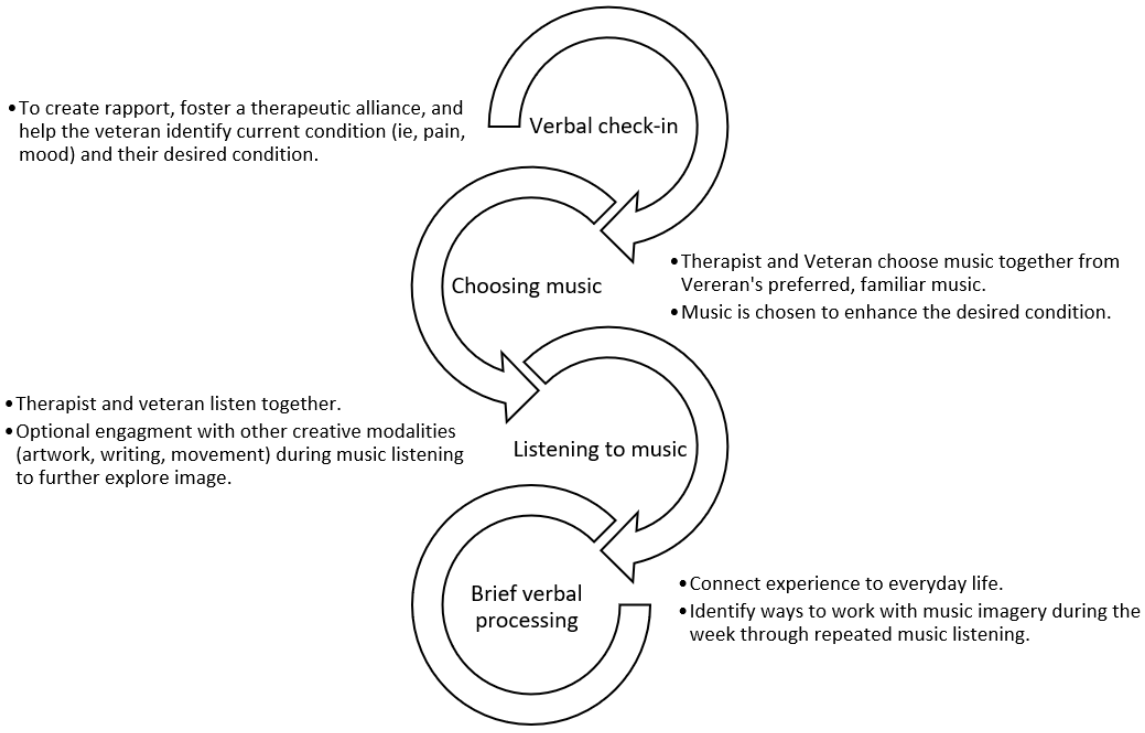
Interventions

Music Imagery Group

Up to 30 participants will be randomized to receive 8 weekly music imagery sessions over 8 to 12 weeks. Allotted time will be up to 12 weeks for treatment to allow for rescheduling if needed. Each session will last approximately 45 minutes. music imagery is derived from Guided Imagery and Music, 1 of the 5 international models of music therapy practice and the most well-known receptive music therapy model [39]. The intervention uses the participant's relationship to music to connect and enhance inner resources and provide a music resource for self-care [40]. Inner resources such as creativity, courage, and serenity connect an individual to their resiliency in the face of conflict, or to overcome some adversity. Resilience is the ability to maintain positive emotional functioning despite physical or psychological challenges [41]. An inner resource may be a visual image of a nurturing figure, the feeling of calming music, or colors that represent strength or a sense of peace. The primary aim in music imagery for chronic pain management is to address participants' relationship to pain, their ability to interact adaptively with chronic pain, and to use supportive and accessible tools (eg, music to self-regulate through relaxation, distraction, and increased connection to inner resources) to manage pain and related psychological symptoms (eg, depression and anxiety) more effectively.

Each music imagery session will be delivered by a board-certified music therapist with specialized training in music imagery. Participants will receive individual therapist-directed sessions. The sessions include 4 steps as illustrated in Figure 3. There is a strong educational component to music imagery, partly met through weekly homework, during which participants are encouraged to *play* with the music and imagery used during the therapist-led session. In this context, *play* refers to the continued engagement with the creative process through repeated listening of music coupled with other modalities (eg, drawing, creative writing, and dancing). The music therapist and veteran identify specific ways to engage with music and imagery between sessions.

Figure 3. Music imagery intervention steps. MI: music imagery.



Music Listening Group

In the music listening arm, a music therapist will meet with the veteran once to identify musical tastes, preferences, and activities; musical memories and social influences; and relationships between music, health, and quality of life [42]. From this meeting, an electronic playlist will be compiled for the veteran to listen to during the 12-week treatment period. The veteran will be asked to maintain a music listening log, including how long they listen, what they listen to, and any reactions to the music (eg, benefits and triggers). Music listening time will not be prescribed, but participants will be encouraged to keep track of their listening to music during the week. Our rationale for including the music listening intervention is to explore whether there is a clinically meaningful change in measures and perceived benefits from a less interactive, less intensive music intervention.

A member of the research team will check in with music listening participants (weekly for the first 3 weeks following their initial session, then biweekly following the 1-month assessment [approximately 7 check-ins in total]) to monitor safety, adherence (ie, time listening to music), and identify other issues.

Control Group: Usual Care

Participants in the usual care group (as is the case for the music imagery and music listening groups) may receive analgesics and nonpharmacological treatments (eg, physical therapy) for chronic musculoskeletal pain. During the study, we will systematically document participants' receipt of usual care in all study arms, including medications, physical therapy, and clinic visits that can help pain (eg, pain specialist, psychologist, and acupuncture). A usual care arm allows us to estimate retention rates of not receiving any active treatment in the trial, informing the choice of a control condition for the planned adequately powered RCT to follow.

Safety and Treatment Fidelity

Listening to music can at times bring up strong emotions, which can increase stress. The potential of this risk is minimal because of the supportive structure of the interventions and the overall study. The therapists are trained to help participants manage any strong emotions that emerge and, if needed, will refer participants for additional psychosocial support.

At each follow-up assessment (1 month, 3 months, and 4 months), a member of the research team will systematically check for participant intercurrent illness, adverse events, and serious adverse events. At all assessments, including baseline, a member of the research team will screen for suicidal ideation guided by a 3-step algorithm consisting of the following: (1) item 9 suicide question of the Patient Health Questionnaire-9 (PHQ-9), (2) the Columbia Suicide Severity Rating Scale Screener if item 9 of PHQ-9 is positive, and (3) Comprehensive Suicide Risk Evaluation for moderate to high risk of suicide based on the Columbia Suicide Severity Rating Scale Screener [43-45].

To ensure intervention fidelity and minimize experimental drift, we will use the following strategies: (1) standardized intervention protocols, study manuals, and training; (2) self-monitoring of intervention sessions recorded in field notes with debriefings across music therapists; (3) quality assurance checklists to track protocol deviations; and (4) therapist field notes documenting session duration and frequency (dose).

Data Collection and Measures

Overview

After obtaining informed consent, the project coordinator will administer a baseline assessment to gather sociodemographic, medical, and psychological comorbidities and prior experience with music; review the patient's treatment history emphasizing previous treatments tried for chronic musculoskeletal pain; and administer measures to assess pain, function, psychological status, and other relevant constructs.

The conceptual framework that informed the choice of study measures is illustrated in Figure 1. The *antecedents* are the patients' pre-existing conditions that will serve as potential covariates. The music interventions are expected to improve outcomes both directly and indirectly through several theoretically derived *mediators*. During therapist-delivered sessions, more engagement is expected to improve mood, enhance therapeutic alliance, and increase self-efficacy, leading to greater independent practice and use of music [17]. Compared with music listening, the music imagery intervention draws upon a patient's inner resources (creativity, courage, and serenity) to improve resilience and perceived benefit. The outcomes are based on a biopsychosocial model of pain and include several measures that encompass the biological, psychological, and social dimensions of pain. The mechanistic pathways depicted offer a theoretical framework for the intervention. Although the pilot is insufficiently powered to find significant mediation, pathway testing will be conducted to help inform the future larger RCT.

Assessments will be conducted by video interviews, unless phone or face-to-face interviews are preferred by the veteran. Assessments of similar lengths have been used by the researchers in several previous trials without overburdening the participants. Following each music imagery session, we will collect brief feedback on the content and delivery of the session. To assess immediate posttreatment effects, we will administer a pre-post visual analog scale to assess change in patient-identified symptoms (eg, pain and anxiety).

We will conduct qualitative interviews with up to 20 veterans following the completion of their last session and assessments with a minimum of 8 participants from each music intervention arm. These interviews will assess the participants' perceptions of the interventions and study participation.

Aim 1 Outcomes

Feasibility metrics include recruitment, retention, completion in allotted time (eg, 12 weeks for the music imagery group), and completion of assessments. The goal is to recruit and enroll 60 veterans into the pilot trial and to complete a median of 80% of all study visits. Those who miss visits will be called upon to ask about barriers to attendance. Individuals who dropped out of the study will be asked what could have been done to improve

their participation. music imagery sessions will occur weekly on a fixed schedule while allowing some flexibility in scheduling for the participant's convenience. The proportion of music imagery participants who complete all sessions within the treatment period will be measured. On the basis of the previous trials, the expected completed outcome assessments rate is 85%.

Acceptability of randomization to study groups will be tracked. Treatment credibility will be assessed for each music intervention and veterans' treatment satisfaction, experience of the interventions, benefits, and barriers or facilitators to study participation will be gathered through qualitative interviews at the end of the treatment period. Safety of the music interventions will be assessed by tracking exacerbations of pain, depression, anxiety, and any adverse events.

Aim 2 Outcomes

The selected measures for aim 2 are outlined in Table 1. The choice of measures is informed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations, our previous studies, the biopsychosocial model, Creative Forces Network's conceptual framework for music therapy, and constructs hypothesized to be affected by the interventions [37].

Table 1. FAMILIA (Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia) patient-centered outcomes: measures and schedule of administration.

Domain	Measure	Schedule			
		BL[a]	1 month	3 months	4 months
Antecedents					
Covariates	Demographics, military history, disability compensation, comorbidity, pain treatments	✓[b]			
Potential mediators					
Therapeutic relationship	Working Alliance Inventory			✓	
Inner resources	State-Trait Assessment of Resilience Scale	✓	✓	✓	✓
Self-efficacy	Arthritis Self-Efficacy Scale	✓		✓	
Outcomes					
Pain intensity	Numeric Rating Scale	✓	✓	✓	✓
Pain interference	Brief Pain Inventory-interference	✓	✓	✓	✓
Pain beliefs	Brief Pain Catastrophizing Scale	✓		✓	
Pain coping	Centrality of Pain Scale	✓		✓	
Pain treatment response	Patient Global Impression of Change		✓	✓	✓
Sleep	PROMIS[c] Sleep Scale	✓	✓	✓	✓
Depression	PHQ-9[d] Depression	✓	✓	✓	✓
Anxiety	GAD-7[e] Anxiety	✓	✓	✓	✓
Trauma	PC PTSD[f] Screen	✓			
Stress	Perceived Stress Scale	✓		✓	
Generic HRQL[g]	EQ-5D	✓		✓	
Social support	Brief Social Support Scale	✓			

[a]BL: baseline.

[b]Check marks indicate when the measure is performed.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

[d]PHQ-9: Patient Health Questionnaire-9.

[e]GAD-7: 7-item Generalized Anxiety Disorder.

[f]PC PTSD: primary care posttraumatic stress disorder.

[g]HRQL: health-related quality of life.

Brief Description of Proposed Measures for FAMILIA Pilot Study

Potential Mediators

The following measures were chosen to explore potential mechanistic pathways for the intervention:

1. Working Alliance Inventory: the Working Alliance Inventory is a measure of the therapeutic alliance that assesses three key aspects of the therapeutic alliance: (1) agreement on the tasks of therapy, (2) agreement on the goals of therapy, and (3) development of an affective bond [46].
2. State-Trait Assessment of Resilience Scale: this new measure assesses resilience with a state and trait approach. Early studies suggest that the State-Trait Assessment of Resilience Scale is a useful measure to track and predict an individual's resilience [47].
3. Arthritis Self-Efficacy Scale: this 8-item scale proved sensitive to change in our trial of low back pain. For each item, patients reported their degree of certainty on a scale ranging from 1 (very uncertain) to 10 (very certain) [48].

Outcomes

The following outcome measures encompass the biological, psychological, and social dimensions of pain:

1. Numeric Rating Scale: this pain intensity scale uses a 0 to 10 numeric rating scale that is anchored with "0"=no pain and "10"=the worst pain imaginable. The Numeric Rating Scale has been validated for specificity and use in chronic pain research [49].
2. Brief Pain Inventory (BPI): the BPI is a multidimensional pain measurement tool with demonstrated reliability in patients with arthritis and other pain conditions. The BPI rates the intensity of pain as well as the interference of pain with mood, physical activity, work, social activity, relationships with others, sleep, and enjoyment of life [50].
3. Brief Pain Catastrophizing Scale: this new brief version of the Pain Catastrophizing Scale has been derived and shows sound measurement properties and strong association with the full 13-item original scale [51].
4. Centrality of Pain Scale: the Centrality of Pain Scale is a 10-item self-report instrument. Responses are measured on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree." In its original validation study, the scale demonstrated high internal consistency (Cronbach α=.90) and good construct validity [52].
5. Patient Global Impression of Change: this is a 15-point, well-validated, global rating scale for evaluating changes in symptoms over time. This scale asks patients to make an initial global assessment of change in their symptoms as "worse," "about the same," or "better." Those who respond that they are "worse" or "better" are asked to make an additional global rating [53].
6. The Patient-Reported Outcomes Measurement Information System Sleep Scale: the Patient-Reported Outcomes Measurement Information System Sleep Disturbance Scale assesses sleep quality and depth, along with difficulties and satisfaction with sleep. Scores are standardized to the general United States adult population on the T-scale with a mean of 50 and SD of 10. Higher scores indicate more symptoms being assessed. A clinically meaningful difference is considered to be ≥5 points [54].
7. PHQ-9 depression: several studies have validated the PHQ-9 as a diagnostic measure with excellent psychometric properties. Internal consistency has consistently been shown to be high (Cronbach α>.80), and test-retest assessment showed the PHQ-9 to be a responsive and reliable measure of depression treatment outcomes [43].
8. 7-item Generalized Anxiety Disorder-Anxiety: the 7-item Generalized Anxiety Disorder has demonstrated reliability (Cronbach α=.89) and validity (criterion, construct, and factorial) as a measure of anxiety in the general population and in primary care [55].
9. Primary Care PTSD Screen: the Primary Care PTSD Screen for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition is used as a screening measure, and is a modified version of the PTSD module of the MINI-International Neuropsychiatric Interview to diagnose Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition PTSD. It has demonstrated strong preliminary results for diagnostic accuracy [56].
10. Perceived Stress Scale: the 10-item Perceived Stress Scale is the most widely used psychological instrument for measuring the perception of stress and has been used in previous music trials [57].
11. EQ-5D-5L: the EQ-5D-5L questionnaire is an instrument for describing and valuing health states and has been used in hundreds of trials. It is a brief self-reported measure of generic health that consists of 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each with 5 levels of functioning [58].
12. Brief Social Support Scale: this reliable and valid short (6-item) scale assesses the emotional and practical dimensions of social support [59].

Data Analysis

As an RCT, it is expected that baseline characteristics of the study participants will be balanced across the 3 treatment groups; however, possible group imbalances will be assessed. Outcomes (feasibility, acceptability, pain, and other patient-centered outcomes) will be reported as means with SDs for continuous variables, or medians (IQRs) for nonlinear data and frequencies with percentages for categorical variables. Changes in pain, associated patient-centered outcomes, and proximal and distal mediators will be explored from baseline to follow-up assessments (1, 3, and 4 months). Bivariate analyses will be performed first to determine if there are significant differences in the 3 treatment groups for the antecedent, mediator, and outcome variables, which will also help to determine if there are group imbalances as discussed above. These analyses will be performed using ANOVA and chi-square tests for continuous and categorical variables, respectively. No post hoc *P* value adjustments will be made, as this is a feasibility study. Data transformations will be used if necessary and Fisher exact test will be used instead of chi-square when expected cell counts are small, with data analyses being performed using SAS software (version 9.4; SAS Institute [60]). Path analyses will

then be performed to examine the path coefficients for the entire conceptual study model (Figure 1). The path coefficients, model fit indices, and covariance structures, along with the results from the bivariate analyses, will be used to determine model adjustments and parameter estimates necessary to determine the power for a larger full study. Path analyses will be performed using Mplus (version 8.7; Muthén & Muthén [61]).

Using guidelines from the thematic analysis by Braun and Clarke [62], the qualitative analysis of veteran interviews and music imagery participant listening logs will occur in 2 broad phases: open coding and focused coding. Open coding facilitates development of a code list for further analysis. In this phase, selected transcripts are read to gain a general understanding of the data and variation across participants. Then, each line will be independently labeled with initial codes to describe the data. The research team will meet to discuss and compare initial codes. The team will then examine the codes, looking for emerging categories to sort and organize the data. As new transcripts are reviewed and coded, categories may be altered or codes are restructured within the categories. This process will occur iteratively until agreement on, and shared understanding of, emergent thematic categories is established. In phase 2, focused coding, the categories derived in the first phase will be applied to transcripts. A subset of transcripts will be coded by all analysts using the agreed-upon categories. Team members will meet in pairs to ensure coding consistency, with discrepancies resolved by consensus. Representative quotations will be presented for each category.

Ethics Approval

FAMILIA was reviewed and approved by the Indiana University institutional review board and the VA research and development committee (IRB #12794).

Results

Participant Involvement in the Research Design

The FAMILIA research team consulted with the VA Health Services Research & Development Service Pain/Opioid Consortium of Research Veteran Engagement Panel facilitation team and outlined a plan for how the panel can inform this project. The panel group includes 12 veterans from across the country who serve as patient advisors to researchers to enhance patient-centered research. All panel members have personal experience with chronic pain or opioids. Veteran members are a diverse group of men and women across a wide age range and include students, retirees, and current workers with varied military, volunteer, and professional experiences. Panel members provided patient-centered feedback that helped inform the study recruitment materials, study design, and anticipated feasibility issues.

Preliminary Data

Members of the research team conducted a single-arm study of 8 veterans with chronic pain to develop and pilot the telehealth MI intervention proposed for FAMILIA. Qualitative data were collected regarding the accessibility and feasibility of virtual delivery and the outcome measures of pain, depression, and anxiety. Findings from this small pilot study helped refine the music imagery intervention and its delivery for FAMILIA. For example, owing to some veterans' lack of technology skills, a technology questionnaire was added to the eligibility screening.

Potential Results and Interpretations

There are several potential results and interpretations from the trial. It is expected that both music interventions will prove acceptable to veterans and that feasibility benchmarks will be reached. However, it is possible that one or both music interventions will not be embraced by all participants or may not meet all specified benchmarks. The qualitative interviews will identify the range of participant perceptions and experiences of both interventions and provide insight into the reasons for unacceptability or feasibility concerns. Although it is hypothesized that both music interventions will be more effective than usual care on pain and associated outcomes, differences in outcome scores may be observed but are unlikely to reach stochastic significance (because FAMILIA is not powered to evaluate efficacy). This potential scenario is acceptable in the context of pilot clinical trials where the primary objective is to field-test logistical aspects of the future RCT and to incorporate these aspects into the study design.

Trial Status

FAMILIA received institutional review board approval in October 2021 and approval from VA Research and Development in November 2021. Recruitment began in March 2022 and as of July 2022, a total of 16 participants were enrolled.

Discussion

The primary purpose of FAMILIA is to examine the feasibility and acceptability of a multicomponent interactive intervention (music imagery) and a single-component, minimally interactive listening intervention (music listening). FAMILIA is not powered to evaluate efficacy, but we anticipate that the music interventions will have a greater effect on outcomes compared with usual care.

Strengths and Limitations

FAMILIA not only addresses the limitations of prior research but also responds to important clinical and research initiatives to develop and test safe and effective nonpharmacological interventions for chronic pain. In clinical practice, analgesics are widely used for pain, but suboptimal pain relief is common as are the side effects. Adverse events related to analgesics, especially nonsteroidal anti-inflammatory drugs and opioids, are well known. Given the modest benefits of analgesics and their safety concerns, novel nonpharmacological options are needed to reduce clinician and patient reliance on analgesics and to reduce the enormous burden of chronic pain on patients.

We selected an active comparator (music listening) to inform whether the design of the subsequent RCT should be a comparative effectiveness trial. We also designed FAMILIA to include a usual care control rather than other comparator options (eg, wait-list control or attention control). A usual care control group is appropriate given the paucity of studies and limited efficacy data of music interventions for chronic pain, especially for virtually delivered interventions. The study sample was

drawn from a single VA medical center and may not be representative of all patients with chronic musculoskeletal pain.

Conclusions

The long-term objective of this research team is to develop and test music interventions that improve chronic pain management and can be implemented in various clinical settings. Findings from FAMILIA will inform refinement of interventions and trial design in advance of conducting a fully powered trial to identify putative mechanisms and test efficacy.

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Data Availability

Owing to privacy and ethical considerations, final data sets underlying publications resulting from this research will not be shared outside the Department of Veterans Affairs, except as required under the Freedom of Information Act.

Authors' Contributions

All authors participated in research design, protocol development, and writing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External review report from grant funders.
[PDF File (Adobe PDF File), 175 KB - resprot_v11i9e38788_app1.pdf]

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Abbreviations

BPI: Brief Pain Inventory
FAMILIA: Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia
ICD 9/10: International Classification of Diseases 9th and 10th editions
PHQ-9: Patient Health Questionnaire-9
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
VA: Veterans Affairs

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Protocol

mHealth Support to Stimulate Physical Activity in Individuals With Intellectual Disability: Protocol for a Mixed Methods Pilot Study

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Abstract

Background: Several studies have shown that individuals with intellectual disabilities (IDs) have low levels of physical activity (PA), and intervention studies on PA suggest inconsistent evidence. The use of technology as a means of motivation for PA has yet to be extensively explored and needs to be further investigated.

Objective: We aim to assess the feasibility and acceptability of procedures for an intervention arm in a future trial on mobile health (mHealth) to support PA for individuals with IDs. In addition, we aim to examine how the use of technology can influence motivation for PA among participants, their caregivers, and staff members.

Methods: A mixed methods pilot study of an intervention arm will be carried out in a planned randomized controlled trial (RCT). Ten participants with ID and their caregivers or a staff member will be included. Information will always be provided by a caregiver or a staff member, or participants with ID if possible. Assessments will be carried out at baseline, follow-up after 4 weeks, and 12 weeks, and include questionnaires on PA, social support, self-efficacy, and challenging behavior. PA will be measured with 2 different activity trackers (Fitbit and Axivity) for 1 week at all assessments. Feasibility will be assessed as recruitment and adherence rate, missing data, usability of the motivational mHealth tool, and estimates of effectiveness. Acceptability of study procedures, activity measures, and motivation for participation in PA will be additionally assessed with qualitative methods at the end of the intervention.

Results: Enrollment commenced in May 2021. Data collection was completed in March 2022.

Conclusions: This pilot study will evaluate the feasibility and acceptability of study procedures of the intervention arm of a planned RCT to address feasibility issues, improve study procedures, and estimate effectiveness of the study measures. How the use of technology can influence motivation for PA will also be examined, which can help guide and improve future PA interventions involving the use of technology.

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KEYWORDS

intellectual disability; physical activity; technology; mHealth; mobile health; exercise; protocol; technology; pilot study; trial; caregivers

Introduction

Physical Activity and Intellectual Disability

Compared to the general population, individuals with intellectual disability (ID) have more sedentary lifestyles, poor health, and greater barriers for participation in physical activity (PA), and consequently lower levels of PA [1-6]. PA is beneficial for cardiovascular and muscular capacity and psychological well-being and can reduce the burden of chronic disease for individuals with ID [1,7-9]. A systematic review by Hassan et al [10] investigated the efficacy of randomized controlled PA interventions, and the results showed inconsistent evidence, with only 3 intervention studies showing a prolonged effect of the intervention [8,10-12]. It is clear that new approaches and further investigations are needed to develop effective interventions for PA in this group.

Including individuals with ID in clinical intervention trials can be challenging, since there are several barriers in all aspects of the research process [13,14]. Struggling to inform the individual with ID about the research, difficulties in obtaining informed consent, finding transport to research sites, and following instructions are common challenges in clinical trials involving individuals with ID [3,15,16]. It is, therefore, particularly important to carefully plan intervention studies for this group, and performing pilot trials or feasibility studies can improve the quality of research [17].

Use of Technology for Individuals With ID

Recent studies have shown measurable benefits from the use of mobile technologies in health care and the use of technology in everyday life has been explored and deemed promising for individuals with ID [18-21]. Although some studies have explored the possibility of using mobile technologies for promoting PA for individuals with ID, there has been only one preliminary report of a randomized controlled trial (RCT) using smartphone support to increase motivation for PA in youths and adults with ID [22-25]. In Norway, many individuals with ID have a smartphone or a tablet device they can use for tailored PA interventions and this use has not been tested. A previous study in this research project showed that individuals with ID are motivated to participate in PA and evince an interest in technology [26,27]. According to the *World Report on Disability 2011* [28], health promotion efforts targeting this population can improve lifestyle behaviors. The report states that these individuals have the right to be included in all PA programs.

Objectives

The primary objective of this pilot study is to assess feasibility and acceptability of study procedures for a future RCT. We also aim to explore the experience of participants and their caregivers regarding the intervention, focusing on success factors, problems, and reasons for dropout, and to understand how the use of technology can influence motivation for PA for this group.

Methods

Study Context

This pilot study is part of a larger project, which aims to develop and test tailored mobile health (mHealth) support systems that promote PA in individuals with ID. We have previously conducted a qualitative study on motivation for participation in PA for such individuals, held workshops and collaborated with developers, and performed usability tests [26,29]. The results from this study will be used in the planning of a larger RCT with 60 participants. See Michalsen et al [27] for more detailed information regarding the RCT.

Design

This protocol describes a mixed methods pilot study of an intervention arm in a planned RCT [27].

Participant Selection and Recruitment

Eligible participants will be identified through their participation in a larger study on health indicators for individuals with ID, the Norwegian Health in Intellectual Disability (NOHID) study, and through staff leaders at municipality levels who have identified potential participants [30]. Overall, 10 participants with ID as well as caregivers and support persons (ie, staff) will be included if they have a sedentary lifestyle or low levels of PA. A sedentary lifestyle is defined as primarily engaging in reading, watching TV, or other mainly sedentary activities. A low level of PA is defined as mainly walking or other light PA for less than 4 hours a week. The number of participants is chosen on the basis of assumptions about sufficient variation for the investigation of feasibility and acceptability of the pilot study [23]. Data saturation of qualitative data collected will be evaluated continually and there will be scope for flexibility to achieve this during the data collection period.

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: (1) low levels of PA, (2) diagnosis of ID (mild, moderate, severe, or profound), (3) aged between 16 and 60 years, (4) ability to participate in the pilot study, (5) capable of walking with or without support, and (6) can provide written informed consent or consent can be obtained from a legal representative. Prior to enrollment, all participants will be screened for readiness, and, if necessary, medical clearance will be obtained. The Physical Activity Readiness Questionnaire will be used for this purpose [31]. Exclusion criteria are as follows: (1) medical contraindications for participation in programs with increased exercise, as advised by the primary care or ID specialist physician; (2) high levels of PA; and (3) inability to provide written informed consent or consent cannot be obtained from a legal representative.

Ethics Approval

All participants and their caregivers will receive information about the purpose and procedures for the study. Informed consent will be obtained from the individuals with ID, as far as possible, if the person has decision-making capability to provide consent. In addition, or in case the person with ID cannot provide consent, a caregiver will provide informed consent on behalf of the person with ID. The definite trial and the pilot study have been approved by the Regional Committees for Medical and Health Research Ethics in Norway (2016/1770) and the data protection officer at the University Hospital of North Norway.

Intervention

The final app is named Active Leisure (Aktiv Fritid) and consists of an advanced activity planner based on the platform developed by the nonprofit organization Smart Cognition AS (Smart Cognition AS). The app offers various interface options (symbols only, easy-to-read text, plain text, and read aloud). See Multimedia Appendix 1 for interface options for the Active Leisure app. The activity planner will mostly be used by an individual with ID and a support person (caregiver or health care provider). Participants will have different levels of functioning and will require different proximity of support persons, which will be considered when delivering the intervention. After completing an activity, a simple reward is available (eg, a smiling face or to share a picture with other users of the app). All activities that go into the activity planner are added through a web application. For this project, the principal author (HM) will be responsible for adding personalized activities into the activity planner for each participant. The use of tailored communication [32] through personalization (the use of the individual's first name in the activity planner), adaptation (individually chosen activities, adjusted communication, including symbols, easy-to-read text, or plain text), preparation and planning, and feedback (rewarding and positive feedback after activities have been performed) are expected to increase motivation and thereby lead to higher levels of PA.

An individual mHealth exercise app has also been developed as a potential alternative that can be added to the Active Leisure planner; this app is called Sorterius (see Multimedia Appendix 2) [33] and is an augmented reality game, inspired by the popular game Pokémon Go. In this app, individuals can use the camera on their phone to look for virtual waste on the ground. Virtual waste will appear as they walk and can be sorted into correct waste bins, depending on the level of difficulty chosen (easy=1 waste bin, medium=2 waste bins, difficult=4 waste bins). When a set number of items has been collected, the individual will receive a virtual reward (stars and positive feedback). It is possible to add goals for steps per day and a weekly goal, which can be tailored to each individual's interest.

Data Collection

Procedure

Three research nurses from the clinical trial unit at the University Hospital of North Norway will support study procedures. Participants will be screened for readiness via telephone. The participants' closest relative or guardian or a support person approved by the participants will be contacted for a baseline assessment via telephone. Questionnaires will be sent over email using the electronic system Research Electronic Data Capture (REDCap), a web-based system that is compliant with relevant regulations and security requirements. The study coordinator will evaluate the data of all participants for completeness. In cases of missing data, respondents will be contacted. Two activity trackers (Fitbit and Axivity), to be worn for 7 consecutive days, will be handed to participants after the baseline assessment. According to the instructions, Fitbit will be used on the dominant hand and Axivity on the nondominant hand. Participants who only accept to use one of the activity trackers will use the Fitbit device, as PA output from this device will be used to assess study outcomes in a later definite trial. After baseline assessments, participants and caregivers or staff will be invited to a goal-setting meeting where the Goal Attainment Scale will be used, and they will be introduced to the mHealth application Active Leisure and a motivating augmented reality application for sorting waste, called "Sorterius" [33]. Caregivers or staff will receive a telephone call from the study nurse at 4-week follow-up and asked to complete the questionnaires via email. The study nurse will also as ask caregivers or staff about the use of the activity trackers and ask for general comments regarding study procedures. These data will be added in the electronic system REDCap. Subsequently, they will receive the activity trackers again. The same procedure will be followed at the 12-week follow-up. Technical support will be available during the study period. After the end of the pilot trial, all participants and caregivers or support persons or staff will be asked to take part in a semistructured interview to share their experiences from the study.

Demographics, Level of ID, and Baseline Functioning

Background data of the participants, such as age, gender, educational level, marital status, living condition, employment status, educational status, job-related or day-center activities, leisure time activities, smoking habits, level of ID (ie, mild, moderate, severe, or profound), genetic diagnosis, medical history or readiness for the PA intervention, and use of medication will be collected at baseline. Ratings of the 5-level Gross Motor Function Classification System and the Communication Function Classification System will also be collected during baseline assessments [34-36].

Qualitative Interview

The recruited participants and their caregivers or a staff member in the pilot study will be asked to participate in a 1-hour qualitative interview after the 12-week follow-up assessment. A semistructured interview will take place at the participant's home or other locations convenient for the participant, caregiver, or staff member [37]. Given the cognitive and speech limitations of many people with ID, semistructured interviews will be performed with the person with ID along with a caregiver or staff member, or only performed with the caregiver or staff member. Therefore, at least for the proxy interviews comprising participants unable to answer the questions, the interviews need to be arranged to facilitate an interpretation that reflects the

participants opinions or attitudes. An interview guide has been developed and will be used in the interviews [26]. The interview guide will be categorized into 2 sections. Section 1 will focus on feasibility and acceptability of procedures, how the mHealth support will be used, and participant and caregiver or staff experiences of participation in all aspects of the study. Section 2 will focus on motivation for using technology to enhance PA levels, how the environment around the person with ID can use technology for PA, and practical barriers for using technology in an everyday setting. All interviews will be audiotaped, transcribed verbatim, and anonymized.

Aspects of Feasibility

To assess feasibility, recruitment, adherence to the intervention, retention, and completeness of data will be evaluated. Recruitment will be evaluated from the number of invited participants, eligible, and recruited or not recruited participants. We expect to include 1-2 eligible participants with ID per week. The expected recruitment rate is 20%; that is, 20% of eligible individuals are expected to agree to be enrolled. Adherence to the intervention will be evaluated through information about the actual use of the applications, which will be obtained from the qualitative interviews. Retention is defined as the number of participants who complete all 3 assessments and the qualitative interview. We expect 80% of the participants to complete the assessments and the interviews. Completeness of quantitative data (missing) will be recorded, and less than 10% data are expected to be missing. Adverse events will be reported to the researchers or the study nurses.

Outcome Measures in the Definite RCT

To assess the planned primary outcome in the definite trial PA level (accelerometer measured steps per day) [26], the participants will use one Fitbit device (Versa). The watch will show a neutral screen during baseline and follow-up assessments. Participants who consent will, in addition, use one device manufactured for scientific purposes (Axivity AX3). Axivity will be used to assess the validity of the Fitbit Versa. This will objectively assess PA and sedentary time [38]. The PA level will be measured for 7 days at each assessment, with a minimum of 3 consecutive days of measurement [8]. Only days with at least 10 hours of wear time will be considered valid [39]. Many of the commercial fitness trackers have been validated for use in the research, including devices from Fitbit [40-42]. The primary outcome in the definite trial will be objectively measured PA assessed by increase in steps per day from the Fitbit device for each participant.

Several secondary outcome measures are explored: minutes of moderate activity, the International Physical Activity Questionnaire Short, BMI, and goal attainment [43-46]. Proxy respondent measures include measures of aberrant behavior (the Aberrant Behaviour Checklist-Community), social support for PA and self-efficacy in a PA setting, and health status (the EQ-5D scale) [47-49]. To control for adverse effects, an adapted quality-of-life scale will be assessed [50]. These measures will be used as evaluation of the sensitivity of the data to detect change and as part of testing the procedures for a later RCT. All these measures have previously been used in research with individuals with ID, and more information about each of these measures can be found in the protocol article for the planned RCT [27].

Data Analyses

Quantitative Data

Appropriate quantitative statistical analyses will be performed using SPSS (version 28; IBM Corp) in accordance with the type and distribution of data. The descriptive statistics are presented as median (IQR) values, means with SDs or 95% CIs, and frequencies of categorical data. The distributional properties of variables will be examined. Hypothesis testing will not be performed. In concordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 extension, estimates of effects using participant outcome measures (differences from baseline to postintervention) will be explored and reported as estimates with 95% CIs without *P* values [51,52]. We shall also perform mixed analyses; quantitative data can be supplemented from information in the qualitative material. For instance, if there is a change in the activity data, interviews can shed light on whether changes are related to the use of technology or whether other mechanisms are involved.

Qualitative Data

The transcribed interviews will be analyzed in accordance with the principles of systematic text condensation [53]. This analysis follows a 4-step procedure. One author will perform the analysis and coding, while the other authors will contribute to further analysis, discussing interview content and preliminary findings, themes, and subthemes. The qualitative approach delivers data on feasibility of procedures, expectations, and the use of applications for PA, experiences with activity trackers and motivation for using technology to increase PA. In addition, clarity and discussion of minor themes and diverse cases will also be included to enhance trustworthiness and transferability to the findings. Reflexivity is a key issue to reflect on the conditions that might corrupt transferability and to adequately interpret the findings [53]. This reflection is imperative, particularly since the authors in this project strongly believe in the need for PA among individuals with ID as well as in the effect of the intervention approach. To facilitate such reflection, the coauthor validation procedure will be important. The consolidated criteria for reporting qualitative research will be utilized to ensure highest possible quality research in this pilot study [54].

Results

Enrollment was initiated in May 2021 and was completed in March 2022. The participants were recruited and administered the intervention individually.

The main contribution of this protocol is a detailed description of a pilot trial that will produce knowledge on how to test procedures of future RCTs for PA among individuals with ID. In addition, this pilot trial will investigate how such individuals can be motivated to use mHealth tools. The trial is registered in ClinicalTrials.gov (NCT04929106).

Discussion

Expected Findings

In this pilot study, a possible main finding will be the large variations in the quality of the collected data. Many intervention studies including individuals with ID have recruitment problems [13], report that data are missing [12], and have a low participation rate, particularly for individuals with severe ID [5,6]. Conducting pilot trials is, therefore, important when planning RCTs since it offers the possibility to address feasibility issues, improve procedures, and prevent wastage of resources in future trials [52]. This knowledge can guide future development of technology-based PA programs and help improve future intervention studies aiming to improve levels of PA.

We expect that this pilot trial will uncover possible challenges in using technological devices for interventions aiming at PA promotion for individuals with ID. This pilot study will show how the use of a technological tool, such as mHealth, can be tested in research involving individuals with ID. The use of technology as a means of improving health has been explored to some extent in this population [20,21,55-57], but limited studies have investigated the use of mHealth for improving levels of PA for individuals with ID [25,58].

The quantitative measurements at baseline and follow-up may reveal differences in PA levels, self-efficacy of PA or in other psychosocial variables. In addition, we expect to find goal achievement among the participants by follow-up. We do not expect to detect any effects of the trial as it is a pilot study [59]. In addition, we expect a possible finding to be that the use of 2 activity trackers, Fitbit and Axivity, will strengthen the quality of activity data. We will gain experience in using one commercial and one research-friendly activity tracker. This experience can be useful in future trials.

In this pilot study, we expect that the use of the mHealth tool will rely on the caregivers or staffs' involvement. The study will, therefore, offer insight into the inclusion of support persons in the planning of PA using mHealth tools, as previous research has shown a greater motivation for PA in individuals with ID if support persons are engaged and included in the activity [26]. It will also explore how the use of goal attainment for adults with ID can be used in a research project on PA promotion [60]. The influence of the use of technology on motivation for PA is being investigated through qualitative methods.

Potential Limitations and Implications

This study will have several limitations. The sample size will be small, which will influence the representativeness of the quantitative data. For the qualitative data, a sample of 10 participants is expected to be of good quality if data saturation is achieved. Another limitation in the data collection can be that having 2 activity trackers might not be accepted by participants, resulting in no measurement if the participants stop using them. Participants or caretakers who agree to be included in the pilot study might be interested or engaged in PA promotion and the variation in the included participants regarding interest in PA might be scarce.

The study has potentially important implications for both individuals with ID and their support networks. The study will be presented at conferences and published in recognized international peer-reviewed journals.

Conclusions

This pilot study will evaluate the feasibility and acceptability of study procedures of the intervention arm of a planned RCT. This can, in turn, address feasibility issues, improve study procedures, and estimate effectiveness of the study measures. We will investigate how technology can be used to influence motivation for PA, which can help guide and improve future PA interventions involving the use of technology. Investigating new ways of enhancing PA for individuals with ID is important to ensure better health and quality of life for this group.

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Data Availability

In this study, participants will not be asked to approve data sharing in the informed consent because some data will include sensitive information, and the small sample makes it possible to identify participants even if the data are deidentified. Moreover, sharing of qualitative data can be difficult. In the ethics committee approval, sharing of data has not been accepted. In future trials, an ethics approval application may include requests for data sharing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshots of the interface options of the Active Leisure app: symbols only, easy to read text, or plain text. The app also has read-aloud capabilities.

[PNG File , 514 KB - resprot_v11i9e37849_app1.png]

Multimedia Appendix 2
Screenshots of the augmented reality application “Sorterius”.
[PNG File , 750 KB - resprot_v11i9e37849_app2.png]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
ID: intellectual disability

mHealth: mobile health
NOHID: Norwegian Health in Intellectual Disability
PA: physical activity
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare (PARTNER-MH), a Peer-Led Patient Navigation Intervention for Racially and Ethnically Minoritized Veterans in Veterans Health Administration Mental Health Services: Protocol for a Mixed Methods Randomized Controlled Feasibility Study

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Abstract

Background: Mental health care disparities are persistent and have increased in recent years. Compared with their White counterparts, members of racially and ethnically minoritized groups have less access to mental health care. Minoritized groups also have lower engagement in mental health treatment and are more likely to experience ineffective patient-provider communication, which contribute to negative mental health care experiences and poor mental health outcomes. Interventions that embrace recovery-oriented practices to support patient engagement and empower patients to participate in their mental health care and treatment decisions may help reduce mental health care disparities. Designed to achieve this goal, the Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare (PARTNER-MH) is a peer-led patient navigation intervention that aims to engage minoritized patients in mental health treatment, support them to play a greater role in their care, and facilitate their participation in shared treatment decision-making.

Objective: The primary aim of this study is to assess the feasibility and acceptability of PARTNER-MH delivered to patients over 6 months. The second aim is to evaluate the preliminary effects of PARTNER-MH on patient activation, patient engagement, and shared decision-making. The third aim is to examine patient-perceived barriers to and facilitators of engagement in PARTNER-MH as well as contextual factors that may inhibit or promote the integration, sustainability, and scalability of PARTNER-MH using the Consolidated Framework for Implementation Research.

Methods: This pilot study evaluates the feasibility and acceptability of PARTNER-MH in a Veterans Health Administration (VHA) mental health setting using a mixed methods, randomized controlled trial study design. PARTNER-MH is tested under real-world conditions using certified VHA peer specialists (peers) selected through usual VHA hiring practices and assigned to the mental health service line. Peers provide PARTNER-MH and usual peer support services. The study compares the impact of PARTNER-MH versus a wait-list control group on patient activation, patient engagement, and shared decision-making as well as other patient-level outcomes. PARTNER-MH also examines organizational factors that could impact its future implementation in VHA settings.

Results: Participants (N=50) were Veterans who were mostly male (n=31, 62%) and self-identified as non-Hispanic (n=44, 88%) and Black (n=35, 70%) with a median age of 45 to 54 years. Most had at least some college education, and 32% (16/50) had completed ≥4 years of college. Randomization produced comparable groups in terms of characteristics and outcome measures at baseline, except for sex.

Conclusions: Rather than simply documenting health disparities among vulnerable populations, PARTNER-MH offers opportunities to evaluate a tailored, culturally sensitive, system-based intervention to improve patient engagement and patient-provider communication in mental health care for racially and ethnically minoritized individuals.

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KEYWORDS

Veterans; health care disparities; intervention; mental health; patient engagement; shared decision-making; patient navigation

Introduction

Background

Low patient engagement in care and ineffective patient-provider communication are 2 major contributors to health care disparities [1-6]. Minoritized patients are less likely to be engaged in care, particularly in mental health care [5-7], which often leads to lower health service use [8-10], higher treatment dropout rates [5,11,12], and worse clinical outcomes [13]. Reasons for low engagement in mental health care vary but include perceived futility of treatment, inadequate access to care, lack of culturally sensitive treatment, low self-efficacy, and lack of trust in health care systems [14-16]. Minoritized patients are also more likely to experience poor patient-provider communication [1,17] and be excluded from treatment decisions [18]. Studies have found patient-provider interactions to be marked by conflicts, perceptions of discrimination, and provider dominance [18]. Ineffective patient-provider communication perpetuates racial health care disparities by contributing to poor care experiences [19-21], low treatment adherence [22], and negative health outcomes [23].

Recovery-oriented practices that prioritize person-centered care, patient autonomy, and empowerment may help reduce health care disparities by engaging patients in services and supporting them to play an active role in their care and treatment decisions [6,14]. Peer support specialists (peers) have been effective in engaging vulnerable populations at risk for treatment dropout, such as patients with serious mental illness, by serving as role models for patients in recovery, addressing stigma associated with mental illness, and providing support [24,25]. Moreover, health services interventions that are tailored to meet the unique needs of minoritized patients by providing culturally sensitive care and addressing patients' social contexts may have a substantial impact [14,26]. One such intervention, patient navigation, is a well-established care model that is effective in reducing barriers to care for minoritized groups by providing personalized navigation services and addressing patients' barriers to care [27-29].

Addressing Mental Health Care Disparities: Piloting the Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare Intervention

To maximize the potential benefits of a culturally sensitive and recovery-oriented approach to patient engagement and communication for minoritized groups, we developed a peer-led patient navigation program—Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare (PARTNER-MH). This manuscript describes the study protocol for a randomized controlled trial to assess the feasibility and acceptability of PARTNER-MH and organizational factors that could impact its implementation in Veterans Health Administration (VHA) settings.

PARTNER-MH Intervention

PARTNER-MH incorporates peer support and patient navigation care models to deliver a manualized patient activation, engagement, and communication intervention to racially and ethnically minoritized Veterans in VHA outpatient mental health clinics. The aims of PARTNER-MH are as follows: (1) to engage racially and ethnically minoritized patients in mental

health care, (2) to increase patient activation by giving patients the tools to become active collaborators in their care, and (3) to improve patients' communication skills and participation in shared treatment decision-making.

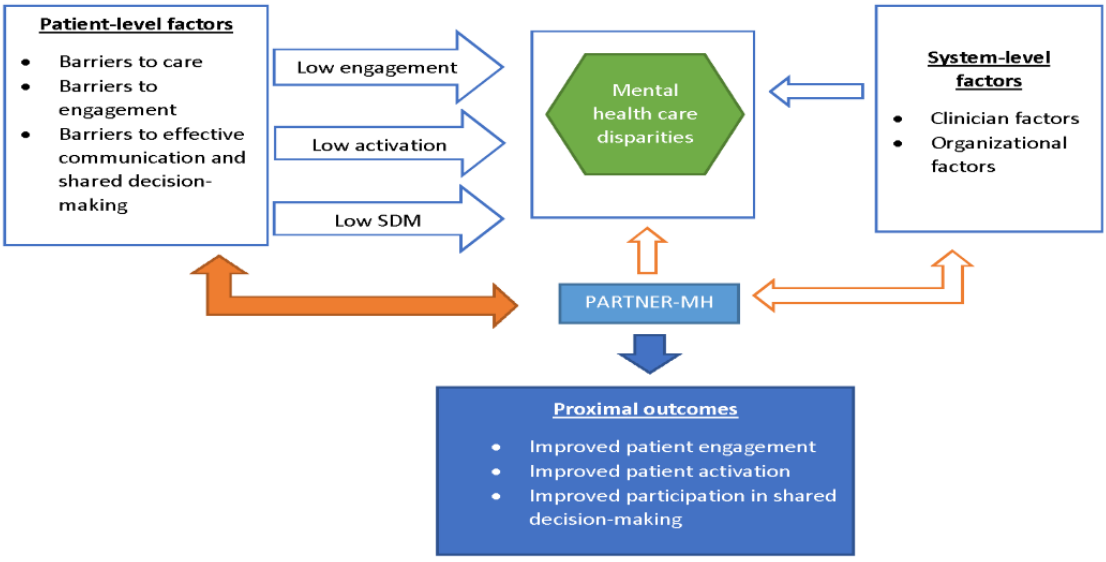
Area of Focus 1: Patient Activation and Patient Engagement

As depicted in Figure 1, PARTNER-MH is designed to reduce mental health disparities by activating and engaging racially and ethnically minoritized patients in VHA mental health services. Although patient activation is closely related to patient engagement and both are often used interchangeably in the literature, they are slightly distinct concepts [30]. Patient activation is an intrapsychic state or cognitive process that is a prerequisite for engagement in care. It is defined as understanding one's role in the care process and having the knowledge, skills, and confidence to manage one's health and health care [30,31]. Patient activation has been linked to positive health outcomes and health care experiences and decreased health care costs. Activated patients self-manage their health, collaborate with care providers, make decisions that affect their health and health care costs, and have the ability to navigate the health care system, obtain preventive care, and participate in proactive behaviors such as regular physical exercise to maintain their health [30]. Patient engagement is the behavioral manifestation of an activated person working in partnership with their care providers to improve their health care experiences and health outcomes. Patient engagement includes patient behaviors demonstrating active participation in care that are shaped by patient-provider relationships and the care environment [16]. In PARTNER-MH, patient engagement involves a continuous and evolving process that begins with treatment seeking, followed by various indicators of ongoing participation in direct care as well as organizational factors that address barriers to care, such as access to services.

To increase patient activation, PARTNER-MH uses a peer support care model to create early and ongoing relationships with patients, develop trust, and empower patients to take charge of their health and health care. PARTNER-MH peers provide education to raise awareness of available services, address patient-level barriers to care such as self-stigma or negative beliefs associated with mental illness and treatment, and provide individualized mental health treatment navigation services to assist with care coordination [6,24,25]. Peers also help patients understand their role in their care, how they can actively partner with care providers to manage their health, and how they can make the most of their participation in mental health services.

PARTNER-MH seeks to facilitate patient engagement by addressing patients' social contexts such as their racial and social identities, living environment, and lived experiences that shape their health and health care experiences. The PARTNER-MH approach to patient engagement also involves addressing negative social determinants of health such as unmet social needs that might be preventing their engagement in care. These include food and housing insecurity, legal issues, and social isolation. Addressing patients' unmet social needs also serves as a catalyst to engage them in conversations about what matters to them as well as social and cultural experiences that may affect their health and health care.

Figure 1. Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare (PARTNER-MH) conceptual model. SDM: shared decision-making.



Area of Focus 2: Patient Communication

Another objective of PARTNER-MH is to improve patients' communication with their providers by identifying and addressing barriers to effective patient-provider communication. This area of focus also includes helping patients prepare for their mental health visits by identifying goals, preparing questions for providers, supporting collaborative relationships with providers, and participating in shared treatment decision-making.

Study Objectives

Aim 1 (primary aim) is to assess the feasibility and acceptability of PARTNER-MH in a VHA mental health care setting.

Aim 2 is to evaluate the preliminary effects of PARTNER-MH on patient activation, patient engagement, and shared decision-making (SDM). We hypothesize that patients randomized to the PARTNER-MH intervention group will report greater patient engagement, patient activation, and SDM than patients randomized to the control group.

Aim 3 is to examine patient-perceived barriers to and facilitators of engagement in PARTNER-MH as well as contextual factors, using the Consolidated Framework for Implementation Research (CFIR) [32], that may inhibit or promote the integration, sustainability, and scalability of PARTNER-MH.

Methods

Design Overview

This pilot study used a convergent mixed methods design [33] that involved a randomized controlled trial comparing the PARTNER-MH intervention with a wait-list control group with a sample of 50 racially and ethnically minoritized Veterans. The wait-list design was selected as a comparator for treatment as usual because it provides patients with the opportunity to participate in the intervention after the wait period, which facilitates recruitment into the study.

PARTNER-MH Interventionists

The interventionists for this pilot study are 2 certified VHA peer support specialists, selected through usual VHA hiring practices and assigned to the mental health service line, who have completed the PARTNER-MH training program. The training program consists of 40 hours of didactic sessions that cover topics such as patient navigation, patient engagement, social determinants of health, diversity and racial discrimination in health care, effective communication, and professional development.

Adherence to Intervention Protocol

Fidelity assessment was conducted quarterly using a sample of 8 patients in the active group (8/29, 28%) stratified by 2 peers. A total of 2 clinical psychologists from the study team used the PARTNER-MH fidelity 17-item checklist and audio-recorded intervention sessions or conducted live participant observations to assess fidelity. Fidelity assessment outcomes were then discussed with peers as well as the steps needed to reinforce or correct deviations from study procedures. In addition, peers receive weekly supervision to reinforce training information, address challenges, and provide support (aim 1).

PARTNER-MH Development and Intervention Structure

PARTNER-MH is a theory-driven, peer-led intervention that was developed using participatory approaches [34,35] guided by the CFIR [32]. Specifically, this process involved the active participation of racially diverse Veterans, peers, and peer supervisors throughout the development and preimplementation phases of PARTNER-MH [36].

PARTNER-MH is a 6-month intervention that consists of individualized sessions with an assigned peer. Sessions are delivered in person, over the phone, or via videoconferencing, depending on patient preferences. Owing to the COVID-19 pandemic and restrictions on in-person visits, most of the sessions were delivered via telehealth. The PARTNER-MH sessions were delivered weekly for the first month, biweekly for the second and third months, and monthly thereafter. Peers and patients also met more often, as needed. The sessions lasted approximately an hour and were tailored to meet patient goals and needs related to engagement, access to services, care coordination, health care communication, and personal support. Peers used the PARTNER-MH handbook to guide and organize their sessions, but they also had the flexibility to use their lived experiences and training to inform the sessions. The flexibility of the PARTNER-MH structure also allowed patients to cover different modules at their own pace. Textbox 1 depicts the modules covered in the handbook and during the sessions.

Textbox 1. Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare (PARTNER-MH) modules.

Getting to know you

- This module covers topics related to social needs assessment (social determinants of health), rapport building, information about patients' social contexts, strengths, racial and other identities, recovery story, and goal setting.

Navigation to Veterans Health Administration mental health services

- Information about Veterans Health Administration metal health services, treatment team composition, treatment options, and how to make the most of services are discussed in this module.

Patient engagement

- This module focuses on ways to be engaged in one's care, discussions of engagement behaviors, and setting goals for being engaged.

Planning your mental health visits

- This module describes the importance of visit preparation, how to prepare for psychiatric medication and therapy visits, and how to set goals for visits that are aligned with one's recovery goals.

Effective patient-provider communication and shared decision-making

- Shared decision-making and effective communication are discussed in this module. Patients role-play with peers and examine barriers to effective communication, strategies to improve communication, and collaboration with providers.

Participants and Setting

PARTNER-MH was offered to racially and ethnically minoritized Veterans receiving mental health services from an outpatient mental health clinic at a large VHA medical center in the Midwest and associated community-based outpatient clinics. The program targeted Veterans across psychiatric diagnostic categories who were relatively new to the broad array but somewhat complicated configuration of VHA outpatient mental health clinics, often requiring help to navigate mental health services. To be eligible for the study, participants must (1) belong to a racially or ethnically minoritized group, (2) be aged ≥18 years, and (3) have a new medication management or therapy appointment scheduled within 12 months before enrollment in the study or have recently re-established treatment after an absence of 2 years. Veterans are excluded if they (1) have mental or cognitive impairments that limited their ability to give consent (eg, having acute psychotic symptoms or being cognitively impaired during the consent or interview process), (2) have hearing difficulties that prevent participation in the interviews, or (3) received medication management services at the clinic for >12 months before enrollment in the study.

Recruitment

Participant recruitment for PARTNER-MH is complete. Multiple strategies were used to recruit participants to capture a diverse group of racially and ethnically minoritized patients. They included inviting eligible patients identified through electronic health records and sending them an introductory letter informing them about the study. The letter gave the participants a method for opting out of further contact. In the absence of such notification, 10 days after the letter's receipt was expected, study staff called the patient to explain the study in greater detail, conduct initial screening, and ask eligible patients whether they wished to participate. Other recruitment strategies included clinician referrals, patient self-referrals, direct advertisements, and snowball sampling (ie, asking enrolled participants to refer others). All eligible patients were given a research packet that included an invitation letter and a study information sheet.

Ethical Considerations

Approval was obtained from the Indiana University Institutional Review Board in November 2017 (1708628270) and the Veterans Affairs (VA) Research and Development review committee. Protocol modifications will undergo further review by the institutional review board, be communicated to the research team, and updated in the clinical trials registry.

Randomization and Protection Against Sources of Bias

Participants completed baseline assessment before being randomized into the study arms to ensure balance and reduce selection bias. Allocation to the treatment arm was carried out using a computer-generated randomization list with randomly varying block sizes of 4 and 8 to maximize allocation concealment. Furthermore, although blinding was not feasible for this project because of the study's limited staffing and the need to collect participant feedback on the feasibility and acceptability of the intervention, study personnel involved in screening and enrollment were masked to the computer-generated randomization assignment and were not included in delivering the intervention. Moreover, peers were not involved in data collection and did not have access to participants' assessment results.

Wait-list Control Structure and Overview

Participants in the wait-list control group received regular VHA mental health services (eg, individual or group psychotherapy, consults, and medication management) for the 6 months after enrollment. To overcome potential issues of contamination, where a peer could deliver PARTNER-MH services to control group participants, participants in the control group were encouraged not to use peer services unless they dropped out of the study. Chart reviews were conducted to assess contamination.

Data Collection Methods, Data Management, and Monitoring

The data collection for this study is ongoing. Screening, enrollment, and survey data were collected and stored via VA REDCap (Research Electronic Data Capture; Vanderbilt University), behind the VA firewall. Outcomes were assessed over the phone at baseline and at 3, 6 (primary end point), 9, and 12 months. Outcome data also included qualitative interviews to evaluate participants' experience of the intervention and organizational factors that may impact its future implementation and the integration of the quantitative and qualitative data. Study participants were compensated with a US $35 gift card for each assessment except for the primary end point (at 6 months), for which they received a US $50 gift card. In addition, because of the COVID-19 in-person visit restrictions, participants received a US $10 gift card for each month they remained enrolled in the study to facilitate access to telehealth delivery of the intervention and retention. A brief exit survey was sent to participants who discontinued the study to evaluate their experiences in the program. Participants' enrollment in the study was recorded in their medical records, which peers had access to. A data safety and monitoring board was also established to evaluate the data quality and safety of the study.

Aim 1 Outcomes and Analysis

Aim 1 is to assess the feasibility and acceptability of PARTNER-MH in a VHA mental health care setting.

The feasibility of PARTNER-MH will be determined based on participants' recruitment, enrollment, and retention rates. Program acceptability for participants will be evaluated using session attendance, number of contacts with peer navigators, and the Patient Satisfaction Survey, which is an 11-item questionnaire rated on a 3-point Likert scale ranging from 1 (not at all) to 3 (very). Satisfaction with the peer was evaluated using a survey that included questions about the patient's relationship with the peer and views of support provided by the peer. Descriptive summaries of recruitment, enrollment, retention, and satisfaction rates will be reported. Participant feedback from qualitative interviews will also be used to inform the feasibility and acceptability of PARTNER-MH (aim 3).

Aim 2 Outcomes and Analysis

Overview

Aim 2 is to evaluate the preliminary effects of PARTNER-MH on patient engagement, patient activation, and SDM.

Aim 2 has three main outcome measures: patient activation, patient engagement, and SDM. In addition, sociodemographic data (eg, age, sex, race, ethnicity, education, and marital status) were collected at baseline. Tertiary and health-related outcomes that included communication self-efficacy, depression, mental health, and physical health functions were also assessed at all time points and are listed in the *Tertiary Outcomes* section.

Secondary Outcomes

The *Patient Activation Measure for Mental Health* (PAM-MH) [37] is a 13-item questionnaire that measures an individual's perceived ability to manage illness and health behaviors. The PAM-MH is reliable, valid, and sensitive to change and correlates with measures of improved self-management and health outcomes. The questions are rated on a 4-point Likert-type scale and then converted using Rasch analysis to a 100-point scale. The PAM-MH has strong test-retest reliability and internal consistency (Cronbach α=.91).

Patient engagement will be assessed using the *Altarum Consumer Engagement (ACE)* measure, a 12-item measure that consists of 3 subscales to reflect patients' commitment to everyday health behaviors, navigation skills in using health care services, and informed choice in treatment decisions [38]. The ACE is administered as a 5-level Likert scale. The subscale scores range from 5 to 25, and the total engagement score is computed by adding the 3 subscale scores and multiplying the sum by 4/3 to obtain a possible range score of 20 to 100. Higher scores represent higher patient engagement.

Finally, we will administer the *SDM-Q-9*, a widely used 9-item patient-reported SDM measure that focuses on the decisional process by rating providers' behaviors in medical encounters. For this study, we will ask participants to think of their most recent visit with their mental health provider. The scale shows good internal consistency (α=.94) and high face and structural validity [39,40]. The SDM-Q-9 is rated on a 6-point Likert scale. The items are scored from 0 to 5 on a 6-point Likert scale ranging from "completely disagree" (0) to "completely agree" (5). A simple sum score with possible values between 0 and 45 is obtained. Item means range from 2.9 to 3.81, and the mean sum of SDM-Q-9 is 3.15 (SD 0.9) [41]. In addition to the SDM-Q-9, we added four questions to evaluate patient participation in treatment decision-making: (1) To the extent that SDM took place during your visit, how much did you drive the process? (2) Thinking about your goal for the visit (what you wanted to be done), how much do you feel you accomplished? (3) How much did you feel heard during your discussion with your provider? (4) Did you experience any barriers that kept you from speaking up or participating in SDM during that visit?

Tertiary Outcomes

Loneliness was assessed using the University of California Los Angeles Loneliness Scale Short Form, a 6-item scale with a 4-point Likert scale ranging from 1 (never) to 4 (often). It has demonstrated internal consistency (α=.89-.94) and test-retest reliability (r=0.73) [42].

The *Perceived Efficacy in Patient-Physician Interaction-5 (PEPPI-5) scale* measures patients' self-efficacy in obtaining medical information and attention to their chief health concern from a physician [43]. The PEPPI-5 is 5-item scale scored on a 5-point Likert scale ranging from 1 (not confident at all) to 5 (very confident). Higher scores indicate higher levels of self-efficacy. The PEPPI-5 has internal consistency (α=.92) and adequate test-retest reliability.

The *Working Alliance Inventory-Short Revised* evaluates three key aspects of the therapeutic alliance between patients and their mental health providers: (1) agreement on the tasks of therapy, (2) agreement on the goals of therapy, and (3) development of an affective bond [44,45]. The *Working Alliance Inventory-Short Revised* includes 12 items rated on a 5-point Likert scale ranging from 1(never) to 5(always). It shows good psychometric properties in both outpatient and inpatient populations, with a reliability of Cronbach α>.90 and convergent validity with the helping alliance questionnaire (r>0.064).

The *Patient Health Questionnaire-9* measures the severity of depressive symptoms. The *Patient Health Questionnaire-9* includes 9 items and demonstrates high internal consistency and reliability (Cronbach α=.89) and good sensitivity and specificity for identifying cases of depression and assessing depression symptom severity [46].

The *Veterans RAND 12-item Health Survey* measures physical function, social function, role limitations owing to physical and emotional problems, mental health, energy and vitality, bodily pain, and the general perception of health. The *Veterans RAND 12-item Health Survey* uses 5-point ordinal response choices and provides two scores: the physical component summary score and the mental health summary score [47].

The *Perceived Discrimination in Healthcare Questionnaire* is a 7-item questionnaire that assesses a respondent's overall health care experiences rather than a specific experience based on their racial background. Respondents are asked to rate their experiences on a 5-point Likert-type scale, with answers ranging from 0 (never) to 4 (always). This questionnaire has shown excellent reliability in diverse patient populations [48].

Veterans' trust in the VA is assessed using a 3-item questionnaire. Responses range from "strongly disagree" to "strongly agree."

Planned Statistical Analyses for Aim 2

Power calculations are provided, but as a pilot, this study is powered only to detect large differences between groups. With a sample of 22 participants in the intervention group and 15 in the wait-list control group, we have 80% power at a .05 significance level to detect an effect size of 0.965 for tests between groups using 2-sided 2-sample t tests. With an estimated SD of 14 for PAM-MH based on previous studies, this sample size will allow detection of a PAM-MH difference of 13.5 between the 2 groups. Within the intervention group, the study can detect an effect size of 0.626 for tests between

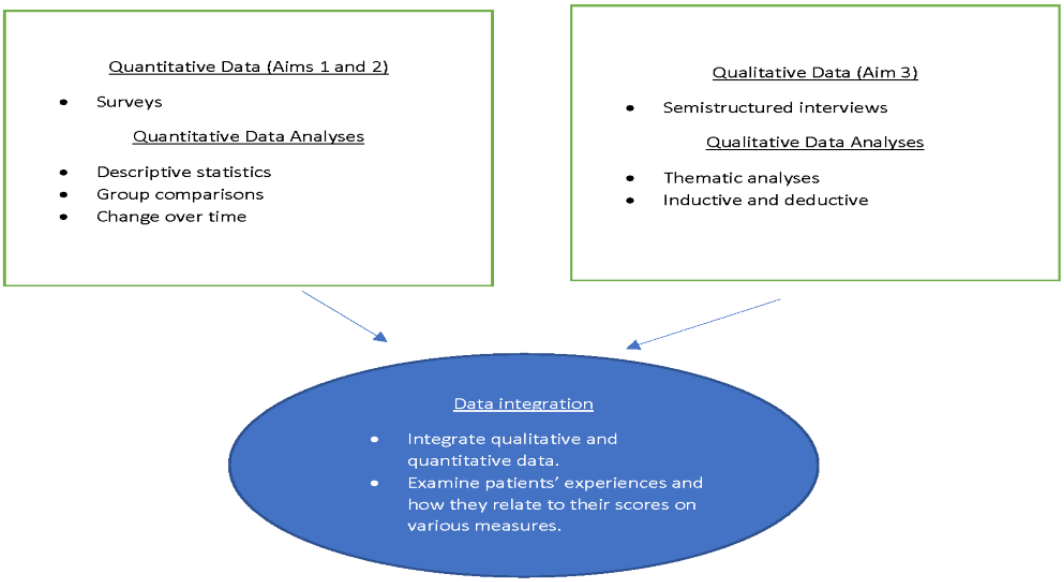
time points using 2-sided paired *t* tests, for a difference of 8.8 for PAM-MH changes. Similarly, in the wait-list control group, the study can detect an effect size of 0.778 and a difference of 10.8 for PAM-MH changes. To account for 25% attrition during follow-up, the study enrolled 30 intervention participants and 20 wait-list control participants.

The internal consistency of each scale for primary and secondary outcomes will be verified in this study sample using Cronbach α. Distributions of the scale scores will be examined to determine whether transformation of the data or nonparametric tests are required for the analyses. In this study, 2-sample *t* tests and Fisher exact tests for continuous and categorical variables, respectively, will be used to compare the demographic and baseline data between participants with and without complete data. Repeated measures ANOVA (RMANOVA) for the scale scores will be used to compare data among the assessments over time. The RMANOVAs will allow different correlations between each assessment time and will allow for the appropriate covariance structure to model the intraparticipant correlations; they will also include a random effect for peers to account for correlation among participants with the same peer. In this intent-to-treat analysis, the RMANOVAs will provide unbiased estimates under the missing-at-random assumption. A 5% significance level will be used for each test.

Planned Mixed Methods Analysis for Aim 2

As depicted in Figure 2, this study uses a convergent mixed methods design [33], which involves simultaneously collecting quantitative and qualitative data and giving equal weight to these data in analyses for the purposes of gaining breadth and depth of understanding (ie, complementarity), identifying whether the qualitative and quantitative data provide the same answer to the same question (ie, convergence), and using qualitative data to expand on unexpected quantitative findings (explanatory) [49-51]. Planned mixed data analysis will involve merging and comparing quantitative and qualitative data in parallel to interpret and explain the findings (QUAL+QUAN). This approach will enable us to triangulate our data by incorporating themes from the semistructured interviews and results from the self-report measures to validate our findings, especially in the context of this feasibility study. Many of the constructs assessed in the quantitative measures will also be explored in the qualitative interviews, for example, intervention characteristics (patient engagement, patient activation, and communication). Moreover, we will use an explanatory mixed methods approach consistent with a randomized controlled trial to better understand the quantitative findings, the process of the intervention, and participants' experiences. The qualitative data will enhance the quantitative analyses by laying the groundwork to better understand the mechanisms of the intervention and facilitate its future implementation.

Figure 2. Joint display for mixed methods data collection and analysis.



Aim 3 Outcomes and Analysis

Overview

Aim 3 is to examine patient-perceived barriers to and facilitators of engagement in PARTNER-MH, as well as contextual factors that may inhibit or promote the integration, sustainability, and scalability of PARTNER-MH using the CFIR [32].

We will use domains of the CFIR [32] to collect and analyze data to inform aim 3. The CFIR offers an overarching typology of five domains affecting intervention development and implementation: (1) intervention characteristics, (2) inner setting, (3) outer setting, (4) characteristics of individuals, and (5) implementation process [32]. Briefly, intervention characteristics include evidence of the intervention and its adaptability. Implementation takes place within an inner setting—the program providing the service. The inner setting is affected by the outer setting—the broader treatment system. Characteristics of individuals such as their skills level also affect intervention delivery and implementation. The implementation process involves different strategies and tools that are used for putting a new practice in place.

Data collection for aim 3 will be guided by the CFIR using semistructured interviews. We will conduct interviews with patients and providers to obtain their perspectives on the intervention and on their experiences of participating in the PARTNER-MH program. Interviews will also assess organizational factors such as time and other resources that may affect the delivery and content of the intervention as well as the impact of the program on Veteran outcomes.

Aim 3 Study Participants

We will invite all 30 Veterans from the intervention group to participate in a qualitative interview. In addition, we will include a purposeful sample of 5 mental health staff members (prescribing and nonprescribing clinicians) with experience in working with peers and patients enrolled in the program.

Aim 3 Planned Qualitative Data Analysis

Interviews from aim 3 will be transcribed, deidentified, and entered into NVivo (QSR International), a qualitative analytical software program, to help organize the data. To facilitate the completion of qualitative data coding and analysis in a short time frame, we will incorporate several features recommended in rapid qualitative assessment [52]. First, we will impose some structure on the data being analyzed. The interviews will reflect CFIR constructs, which will allow for easier access to apply coding. Second, we will incorporate selected codes a priori, based on our prior research, to provide initial structure to the coding process, but will also allow for the expansion of the code list in which other meaningful ideas may emerge. We will use an inductive, interpretive approach that borrows concepts from grounded theory, to identify and explore emerging areas not covered by interview guidelines.

Through an iterative, consensus-building process, we will review transcripts to identify emergent themes consistent with techniques of immersion and crystallization [50]. We will independently read a few selected documents to identify possible areas of pursuit. We will create episode profiles for each transcript to facilitate in-depth understanding of each case and identify emerging themes for cross-transcript comparison. We will meet to discuss our findings and develop a working set of codes to add to the structural codes mentioned earlier. We will repeat this process on fresh sets of documents until we have a set of defined codes that are stable and consistent. We will then code individual transcripts independently.

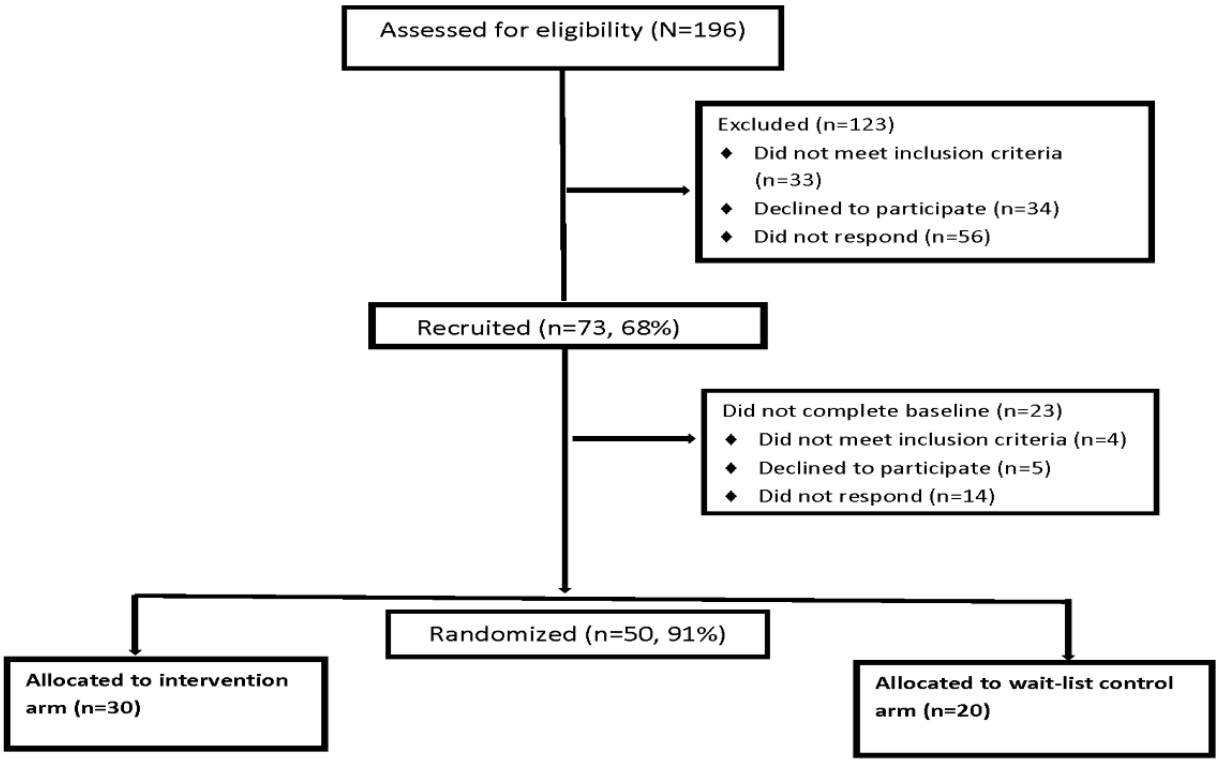
To facilitate the rigor of the data analysis process, we plan to hold regular meetings with the coding team to examine coding across analysts, resolve differences in coding, identify and resolve coding drift, and conduct iterative refinement of code definitions. We will maintain memos of our coding processes, coding decisions, and analyses. We will also continually assess and maintain consistency and consensus in our coding practices [50].

Results

Overview

Figure 3 shows the results of the screening, eligibility determination, enrollment, and randomization of participants, conducted from August 17, 2020, to April 12, 2021. To recruit participants, we mailed letters to 191 potential participants. In addition, 5 patients were referred by clinicians or self-referred through study advertisements or word of mouth. Of these participants, 56 (29%) were not able to be reached to screen for eligibility, 33 (17%) were found to be ineligible, and 34 (17%) declined to participate. Of the interested participants, 73 (68%) met the eligibility criteria. However, 14 (19%) of these participants either canceled or did not show up for their baseline after rescheduling, 4 (5%) declined to participate in the study, and 4 (5%) were deemed ineligible because of changed circumstances such as relocating to a different state or transferring health services outside the VHA. Overall, 50 participants were enrolled in the study, with 30 (60%) randomized to the PARTNER-MH group and 20 (40%) randomized to the wait-list control group.

Figure 3. Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



Baseline Data

Participant demographics are presented in Table 1. The participants were mostly male (31/50, 62%) and self-identified as Black (35/50, 70%) and non-Hispanic (44/50, 88%). Participants were almost evenly distributed across three age groups: 25- to 34 years (12/50, 25%), 45 to 54 years (14/50, 28%), and 55 to 64 years (12/50, 24%), and 48% (24/50) had some college education. Randomization produced comparable groups with regard to baseline characteristics of age, race, ethnicity, and education. However, the wait-list control group had more female participants (11/20, 55%) than the active intervention group (8/30, 27%; *P*=.04). As shown in Tables 2 and 3, the 2 groups were also comparable on the outcome measures at baseline.

Table 1. Participant demographics.

Demographics	Overall (N=50), n (%)	Intervention group (n=30), n (%)	Wait-list control group (n=20), n (%)	*P* value
Age (years)				.31
18-24	1 (2)	0 (0)	1 (5)	
25-34	12 (24)	8 (26.7)	4 (20)	
35-44	9 (18)	7 (23.3)	2 (10)	
45-54	14 (28)	6 (20)	8 (40)	
55-64	12 (24)	7 (23.3)	5 (25)	
65-75	2 (4)	2 (6.7)	0 (0)	
Race				.21
White	3 (6)	3 (10)	0 (0)	
Black	35 (70)	20 (66.7)	15 (75)	
Asian	1 (2)	0 (0)	1 (5)	
Other	5 (10)	2 (6.7)	3 (15)	
Multi	6 (12)	5 (16.7)	1 (5)	
Hispanic	6 (12)	4 (13.3)	2 (10)	.72
Sex				.04[a]
Male	31 (62)	22 (73.3)	9 (45)	
Female	19 (38)	8 (26.7)	11 (55)	
Education				.07
HS[b] or GED[c]	10 (20)	3 (10)	7 (35)	
Some college or 2 year degree	24 (48)	17 (56.7)	7 (35)	
4-year college degree	9 (18)	7 (23.3)	2 (10)	
>4 years college	7 (14)	3 (10)	4 (20)	

[a]Statistically significant.

[b]HS: high school.

[c]GED: General Educational Development.

Table 2. Baseline secondary outcome measures.

Measures	Overall (N=50)	Intervention group (n=30)	Wait-list control group (n=20)	*P* value (95% CI)
Altarum Consumer Engagement Commitment to Everyday Health Behavior subscale, mean (SD)	13.7 (5.2)	13.7 (4.7)	13.6 (5.9)	.91
Altarum Consumer Engagement Informed Choice subscale, mean (SD)	10.5 (5.0)	10.6 (4.8)	10.4 (5.4)	.89
Altarum Consumer Engagement Navigation subscale, mean (SD)	15.2 (3.8)	15.5 (4.4)	14.8 (2.8)	.41
Patient Activation Measure for Mental Health Activation scores, mean (SD)	51.5 (11.3)	52.8 (11.0)	49.6 (11.8)	.38
SDM-Q-9[a], mean (SD)	26.8 (9.4)	25.8 (9.1)	28.3 (9.7)	.23
SDM-Q-9 question 10, n (%)				.86
Not at all	10 (20)	6 (20)	4 (20)	
A little	10 (20)	6 (20)	4 (20)	
Some	9 (18)	4 (13)	5 (25)	
A lot	15 (30)	10 (33)	5 (25)	
N/A[b]	6 (12)	4 (1)	2 (10)	
SDM-Q-9 question 11, n (%)				.91
Nothing at all	7 (14)	5 (16.7)	2 (10)	
A little	16 (32)	9 (30)	7 (35)	
Some	12 (24)	7 (23.3)	5 (25)	
A lot	11 (22)	6 (20)	5 (25)	
Every goal set	4 (8)	3 (10)	1 (5)	
SDM-Q-9 question 12, n (%)				.06
Not at all	4 (8)	4 (13.3)	0 (0)	
A little	4 (8)	0 (0)	4 (20)	
Some	9 (18)	5 (16.7)	4 (20)	
A lot	22 (44)	14 (46.7)	8 (40)	
Completely	11 (22.2)	7 (23.3)	4 (20)	
SDM-Q-9 question 13, n (%)				.97
Yes	16 (32)	10 (33.3)	6 (30)	
No	29 (58)	17 (56.7)	12 (60)	
Unsure	5 (10)	3 (10)	2 (10)	

[a]SDM-Q-9: shared decision-making-9.

[b]N/A: not applicable.

Table 3. Baseline tertiary outcome measures.

Secondary measures	Overall (N=50), mean, (SD)	Intervention group (n=30), mean, (SD)	Wait-list control group (n=20), mean, (SD)	*P* value
University of California, Los Angeles Loneliness Scale	16.2 (5.2)	17.1 (4.2)	14.8 (6.3)	.22
Perceived Efficacy in Patient-Physicians Interaction-5	35.7 (10.8)	35.2 (10.6)	36.4 (11.4)	.61
Working Alliance Inventory-Short Revised	39.8 (14.2)	38.0 (15.4)	42.6 (11.9)	.39
Perceived Discrimination in Healthcare Questionnaire	7.3 (5.8)	7.9 (5.9)	6.4 (5.7)	.30
Patient Health Questionnaire-9	13.6 (6.5)	14.9 (6.4)	11.5 (6.3)	.05
Veterans RAND 12-item Health Survey Physical Health	41.6 (7.7)	41.7 (7.2)	41.5 (8.8)	.98
Veterans RAND 12-item Health Survey Mental Health	32.4 (8.2)	31.0 (9.2)	34.7 (5.8)	.06

Data Collection

Data collection for the trial ended in May 2022. Data analysis is projected to be completed by December 1, 2022.

Discussion

Overview

This pilot study aims to evaluate the feasibility, acceptability, and preliminary effects of a peer-led patient navigation intervention for racially and ethnically minoritized Veterans in VHA mental health clinics. We anticipate that the findings of this study will help identify barriers to and facilitators of the delivery of the intervention, its feasibility in VHA clinical settings, and its acceptability to the study participants. This pilot study will also facilitate the evaluation of the preliminary impacts of the intervention on patient engagement, patient activation, SDM, and related health outcomes.

Mental health care disparities are persistent and contribute to increased comorbidities, mortality, and health care cost expenditures among individuals of racially and ethnically minoritized backgrounds [53-55]. Minoritized patients experience lower activation, lower engagement, and lower participation in SDM, all of which have been implicated in negative health care experiences and health care outcomes for these groups [7,56,57]. Improving patient engagement, activation, or participation in SDM may lead to improved mental health outcomes and mental health equity in minoritized groups.

To move beyond the documentation of disparities, PARTNER-MH was designed to leverage the potential of peer support and patient navigation care models to effectively improve patient engagement, activation, and participation in SDM in mental health care among patients of minoritized backgrounds. PARTNER-MH uses a social determinant health care framework by assessing patients' unmet social needs to engage them in care and learn about their lived experiences and social contexts. The additional focus of PARTNER-MH on improving patients' communication self-efficacy and participation in SDM may contribute to improved satisfaction with services, treatment adherence, and outcomes. The program's delivery over 6 months may also increase the percentage of patients who become engaged in care and achieve their mental health goals.

This feasibility trial will also help identify potential unanticipated challenges in the program and its implementation. For instance, it may help identify patients who may benefit the most from this intervention and the optimal length of intervention to facilitate sustained engagement in the program. It may also help identify interventionist characteristics and setting contexts that are most appropriate for this intervention.

Limitations

A limitation of this study is that participants were not blinded to the study conditions, which may have affected participant behaviors and study outcomes. Moreover, PARTNER-MH is a patient-facing intervention, which may limit its impact on provider behaviors and ultimately, patient participation in collaborative treatment decision-making with their providers. Although this is a potential limitation of the intervention, other studies have shown that patient-focused interventions have some success in improving patient-provider communication and reducing health care disparities. For example, a patient-coaching intervention was shown to reduce patient-provider miscommunication and disparities in pain control among minoritized patients [58]. By supporting patients' active engagement in care and fostering communication self-efficacy, PARTNER-MH may contribute to patients' increased engagement in shared treatment decision-making. PARTNER-MH represents a novel approach that may help advance health equity for minoritized patients and represent a new system-based model to create sustained engagement of minoritized groups in mental health care.

In addition, as PARTNER-MH focuses on patient engagement, activation, and patient-provider communication—issues that are cross-cutting among other disease populations—the lessons learned in this study could be applied to minoritized patients with other chronic health conditions in other settings. PARTNER-MH also offers the potential to advance the field of peer support and patient navigation by creating a training program for VHA peer support specialists to deliver peer-led navigation services in outpatient mental health clinics over 6 months.

Strengths of This Study

The mixed methods approach is a strength of this study that will help evaluate participants' experiences of the intervention and identify areas of improvement and contextual factors that could influence its future implementation. In addition, the

feasibility of PARTNER-MH is tested under real-world conditions such as using existing VHA hiring procedures and assigning study peers to the mental health organizational chart with mixed roles to provide PARTNER-MH and usual peer support services. This aspect of the study approach is also a strength that should provide rich implementation information for future consideration.

Future Directions

This pilot study will lay the foundation for future testing of PARTNER-MH and contribute to mental health disparities intervention research that targets underrepresented, minoritized patients. The proposed study will provide preliminary data for a larger trial to examine the effectiveness of PARTNER-MH. On the basis of the findings of this pilot study, future studies may also address a broader array of clinical and health services outcomes such as the impact of PARTNER-MH on patients' use of mental health services and treatment outcomes. They may also identify potential implementation strategies for PARTNER-MH and evaluate its economic impact on the health care expenditure of the VHA. Future trials are also needed to determine the broad-based acceptance and effectiveness of PARTNER-MH across diverse VA facilities.

Dissemination Plan

The results of this study will be made available to health care professionals, researchers, and the public through publications, academic conferences, and other presentations. Study results will also be presented to VHA patient engagement boards, clinical partners, and other stakeholders.

Conclusions

The outcome of this study will establish the feasibility and acceptability of PARTNER-MH, a peer-led patient navigation intervention to improve patient engagement, patient activation, and participation in SDM among racially diverse Veterans in mental health clinics. If the findings of this pilot study are positive, they will provide support for rigorous testing of PARTNER-MH in a larger trial. If found to be effective then, PARTNER-MH will significantly affect the mental health care experiences and outcomes of racially diverse patient populations. Moreover, as a peer-led intervention, PARTNER-MH could be promoted as a potentially easily scalable approach to increase mental health equity.

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Data Availability

Data are not available to share due to Department of Veterans Affairs and ethical retractions; however, annotation instructions and vocabulary are available upon request.

Authors' Contributions

JE, DJB, ALR, SP, TD, MJB, MPS, MS, MC, and MSM made substantial contributions to the conception or design of the work and to data interpretation. JE, CO, KW, DSZ, EA, and JES contributed to the data collection and analysis. JA and JM were the study interventionists and contributed to the refinement of the intervention. JE wrote the initial draft of the manuscript. All authors have read, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACE: Altarum Consumer Engagement
CFIR: Consolidated Framework for Implementation Research
PAM-MH: Patient Activation Measure for Mental Health
PARTNER-MH: Proactive, Recovery-Oriented Treatment Navigation to Engage Racially Diverse Veterans in Mental Healthcare
PEPPI-5: Perceived Efficacy in Patient-Physician Interaction-5
REDCap: Research Electronic Data Capture; Vanderbilt University
RMANOVA: repeated measures ANOVA
SDM: shared decision-making
VA: Veterans Affairs
VHA: Veterans Health Administration

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Protocol

Development of an HIV Prevention Intervention for African American Young Men Who Have Sex With Men (Y2Prevent): Study Protocol

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Abstract

Background: African American young men who have sex with men (YMSM) possess many intersecting identities that may increase their vulnerability to social stigmatization and discrimination, which yields a negative influence on their well-being and behaviors. These experiences often manifest as increased general and sexual risk-taking behaviors that place this particular group at an increased risk for HIV. This scenario is exacerbated by the lack of HIV prevention interventions specifically designed for African American YMSM.

Objective: In this paper, we discuss the development of research designed to refine, pilot, and evaluate the feasibility, acceptability, and preliminary efficacy of a behavioral intervention designed to build resilience and reduce substance use and HIV risk behaviors among African American YMSM. The overarching aim of this research, funded by the National Institutes of Health, is to further refine and pilot test an intervention called Young Men's Adult Identity Monitoring (YM-AIM). YM-AIM is a theory-driven, group-level intervention designed to help African American YMSM develop a healthy vision for their future (or *possible future self*) by defining a set of short-term and long-term goals in the areas of education, health, family, and intimate relationships.

Methods: Through partnerships with community members and community-based organizations, we will further strengthen and refine YM-AIM to include 3 new components: biomedical HIV prevention strategies (pre-exposure prophylaxis and postexposure prophylaxis); HIV and sexually transmitted infection (STI) testing and HIV care referral, drug screening, and drug treatment referral; and a youth mentoring component. We will recruit African American YMSM, aged 18 to 24 years, into 2 working groups; each group will consist of 6 to 8 members and will convene on a weekly basis, and each meeting will focus on one specific YM-AIM topic. This feedback will be used to further refine the intervention, which will then be evaluated for its feasibility and acceptability. Intervention outcomes include drug use in the past 30 days and 3 months, alcohol use, condomless sex, number of sex partners, and increasing condom use intention, condom use self-efficacy, HIV and STI testing recency and frequency, and linkage to care.

Results: As of June 2022, we completed phase 1 of Y2Prevent and launched phase 2 of Y2Prevent to begin recruitment for working group participants. Phase 3 of Y2Prevent is anticipated to be launched in September and is expected to be completed by the end of this project period in December 2022.

Conclusions: Few youth-focused interventions have sought to help youth identify and develop the skills needed to navigate the social and structural factors that contribute to individual-level engagement in prevention among sexual minority youth. This research seeks to promote young men's adoption and maintenance of HIV-protective behaviors (eg, safer sex, pre-exposure prophylaxis use, HIV and STI testing, and health care use).

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KEYWORDS

young men who have sex with men; YMSM; African American; resilience; mentoring; HIV prevention

Introduction

Disproportionate Impact of HIV on African American Young Men Who Have Sex With Men

Men who have sex with men, including gay and bisexual men, possess many intersecting identities that may relate to their gender, sexual orientation, and ethnic and racial identities. Although lesbian, gay, bisexual, transgender, queer (or questioning), asexual (or allied), and intersex (LGBTQAI) communities have traditionally been affected by stigma and low social acceptance, a particular risk of experiencing stigmatizing events exists for LGBTQAI people who also identify with a minority ethnic or racial group. Individuals with multiple minority identities oftentimes experience increased daily stigmatization and discrimination, which yields a negative influence on their well-being and behaviors [1,2].

Syndemics is a concept used to describe this disproportionate risk for increased stigma and negative health outcomes [3]. Syndemics are defined as ≥2 epidemics interacting in synergy, such that they exacerbate health consequences owing to their interaction with one another or with structural factors [3]. For members of the LGBTQAI community who also identify with minority racial or ethnic groups, this may translate to enduring the compounded effects of experiencing stigma in many forms including homophobia, racism, and discrimination.

For example, when compared with White and Latino individuals, Black or African American young men who have sex with men (YMSM) are more likely to experience violence and victimization in numerous settings, including home, work, and school, on account of their sexual identities, attractions, race, and ethnicity [4]. These experiences are significantly associated with adverse health outcomes, including illicit drug use, alcohol misuse, and risky sexual behaviors, which are known to increase the risk of HIV infection [5,6]. These findings partially explicate this historical disparity in which African American YMSM have been reported to be 5 times more likely to be HIV positive, 7 times more likely to have an undiagnosed HIV infection, and 45% more likely to be diagnosed with a sexually transmitted infection (STI) than other YMSM [7]. Among African American YMSM, the rates of those living with HIV are estimated at 52% for those aged 13 to 24 years [8].

Current HIV Prevention Efforts

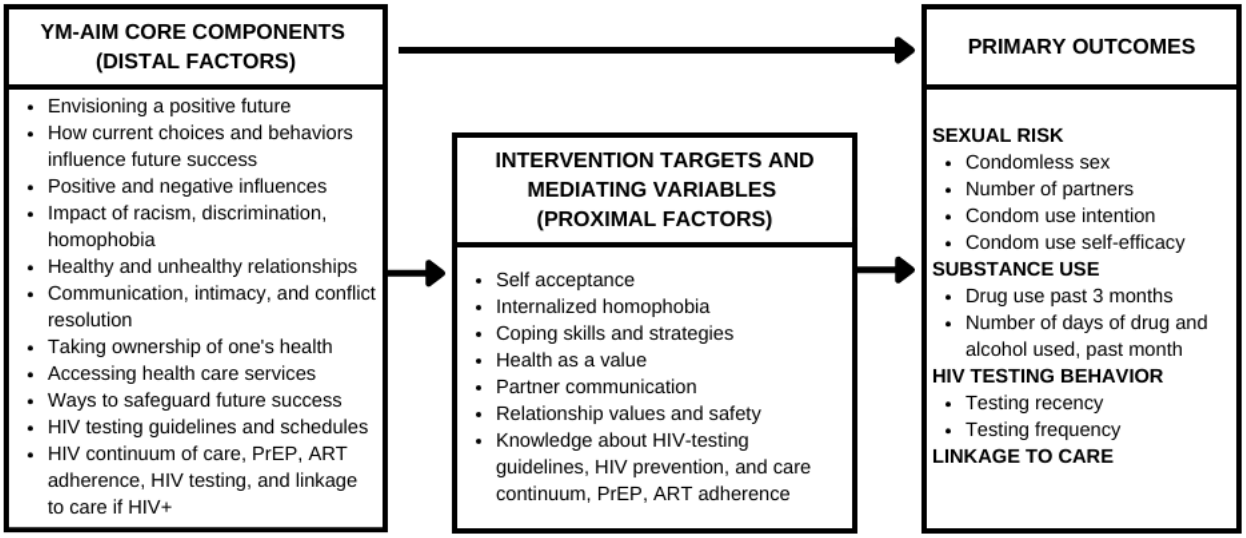
The Centers for Disease Control and Prevention (CDC) HIV and AIDS Prevention Research Synthesis Project identifies evidence-based interventions (EBIs) and evidence-informed interventions for their compendium of EBIs and best practices for HIV prevention [9]. The compendium identifies 60 EBIs for HIV and sexual risk reduction and intends to help HIV prevention interventionists choose interventions that are more appropriate for their population of interest. However, only one-third of the EBIs are designed for adolescents or young adults, and only two—Mpowerment and Young Men's Health Project—are specific to YMSM, but neither addresses the unique risk profiles for African American YMSM, as has been described in the literature [10].

Furthermore, novel prevention approaches such as pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) have enormous potential to limit the spread of HIV by reducing an individual's susceptibility. However, data show that as little as 12% to 14% of all YMSM currently use PrEP, with uptake being much lower among African American YMSM at 4.7% [11,12]. Among African American YMSM, barriers to PrEP uptake include low prioritization and interest in PrEP, low perceived risk of HIV acquisition because of feeling invincible and trusting sex partners, lack of information about how and where to access PrEP, and general stigma surrounding PrEP use [13]. This suggests the need for more evidence-informed interventions to increase awareness of HIV prevention strategies and to guide perceptions of risk, access, and prioritization of biomedical HIV prevention approaches.

Young Men's Adult Identity Monitoring to Y2Prevent: Opportunities to Turn the Curve of the HIV Epidemic

To curb HIV incidence in African American YMSM and with funding from the National Institute on Drug Abuse (grant R21DA024588), we developed and pilot-tested an intervention called Young Men's Adult Identity Monitoring (YM-AIM). YM-AIM integrated concepts from an existing CDC EBI, initially targeting Black and African American adolescent girls [14]. YM-AIM is a theory-driven, group-level intervention designed to help African American YMSM develop a healthy vision for their future by defining a set of short-term and long-term goals pertaining to education, health, family, and intimate relationships. YM-AIM was developed based on findings from the literature that suggest that compared with White and Latino YMSM, experiences of racism and homophobia and exposure to violence and victimization from family, intimate partners, and their community put African American YMSM at significantly greater risk for illicit drug use, HIV and STI acquisition, and mental health challenges [4,15]. Specifically, YM-AIM focused on (1) identifying and developing goals related to education, employment, and healthy relationships and (2) identifying behaviors and barriers, such as drug use, sexual risk, and abusive relationships that get in the way of achieving these goals. YM-AIM activities encouraged participants to consider how their involvement in risky behaviors, including illicit drug use, condomless sex, and multiple sex partners, may interfere with achieving their goals (Figure 1) [16].

Figure 1. Young Men's Adult Identity Monitoring (YM-AIM) main components and outcomes. ART: antiretroviral therapy; PrEP: pre-exposure prophylaxis.



Our initial pilot group of YM-AIM consisted of 36 participants. We collected feedback on the participants' experiences through postintervention assessments and exit interviews. The findings highlighted that the participants reported wanting and needing ongoing social support after completing the intervention to help them achieve their short-term and long-term goals and to help them maintain positive changes in risky sexual behavior. We learned to update YM-AIM from this formative work and incorporate strategies to create sustained support for participants, specifically by including a mentoring component, as suggested by YM-AIM pilot group participants. This novel mentoring approach is supported by findings that highlight that by introducing youth to new experiences and sharing positive values, mentors can help young people avoid negative behaviors; reduce the risk of delinquency, aggression, and drug use; and lead to increased academic satisfaction and performance [17,18].

Feedback from the pilot testing of YM-AIM suggested the need to further refine YM-AIM to include a mentoring component designed to provide ongoing support and reinforcement of behavior change even after completing the intervention. Therefore, we obtained a second grant from the National Institute on Drug Abuse (grant R34DA044106) to further refine YM-AIM, which included updating the content of the intervention and incorporating activities about new advances in biomedical HIV prevention, namely, PrEP and PEP. This update was necessary to remain current with HIV prevention strategies and resulted in a new HIV prevention intervention named Y2Prevent.

Y2Prevent included three new components: (1) biomedical HIV prevention strategies (ie, PrEP and PEP); (2) HIV and STI testing and HIV care referrals and drug screening and drug treatment referral; and (3) a youth mentoring component through a partnership with the Los Angeles LGBT Center.

Y2Prevent Overarching Goals and Specific Aims

The overarching aim of Y2Prevent is to develop a culturally tailored and developmentally appropriate behavioral intervention designed to reduce substance use and risky sexual behaviors among African American YMSM aged 18 to 24 years. The specific aims were as follows: (1) conduct formative research to develop Y2Prevent and refine our assessment measures, (2) finalize Y2Prevent study protocols and consent forms and develop a manual of operations, and (3) pilot test and evaluate Y2Prevent to determine intervention feasibility and acceptability and collect preliminary efficacy data.

Y2Prevent has several key objectives related to African American YMSM, which include promoting resilience; building social skills and assets; increasing skills by recognizing and navigating individual, social, and structural barriers leading to risk; adopting and maintaining protective behaviors such as engaging in safe sex; and using PrEP or PEP and HIV and STI testing services. Intervention outcomes include reductions in drug use, alcohol use, condomless sex, number of sex partners, and an increase in condom use intention, condom use self-efficacy, HIV and STI testing recency and frequency, uptake and adherence of PrEP, and linkage to care.

In this study, we describe the approach used to refine the YM-AIM intervention to bring an additional component (mentoring) and additional content (eg, PrEP). We also discuss the proposed approach to evaluate the feasibility, acceptability, and preliminary efficacy of the new intervention, Y2Prevent.

Theoretical Foundation: Positive Youth Development and Resilience Theory

The Positive Youth Development and Resilience Theory provides a robust and innovative framework for examining YMSM who experience significant exposure to syndemic and social health disparities [19,20]. In health behavior, syndemics are linked to health problems that occur among specific groups because of personal (eg, higher anxiety or depression) or environmental conditions (eg, disease concentration and lack of resources) that interact and produce negative effects on individuals [21]. A large body of research on YMSM uses a syndemic framework to understand the health and social

inequalities affecting them, as well as the increased sexual and risk-taking behaviors that are usually associated with these disparities [22-26]. The current findings show that enhancing assets and resources that promote resilience and reduce environmental barriers may reduce risk factors and increase the uptake of HIV prevention services.

Resilience theory is a conceptual framework for understanding how individuals can bounce back into life after experiencing an adverse situation using a strength-focused approach [20]. Resilience theory argues that syndemic factors alone do not create an effect on individuals but that negative effects also depend on how individuals respond, suggesting that interventions should focus on raising awareness of and access to tools and strategies to buffer against syndemic factors. Findings have shown that resilience resources, such as employment, behavioral coping strategies, cognitions and emotions, and positive relationships, are all associated with lower HIV risk [27]. In particular, a study that investigated the association of resilience-based factors with PrEP uptake among African American YMSM found that factors such as the presence of a parental figure within an individual's network were predictive of a greater likelihood of PrEP use, indicating that social support from close personal networks should be leveraged to improve HIV prevention and engagement services among African American YMSM [28].

Methods

Ethics Approval

This study has been reviewed and approved by the institutional review board of Children's Hospital Los Angeles (number 10-00029).

Study Design

The refinement of the YM-AIM intervention will be conducted in 3 phases. Institutional review board approval will be obtained before conducting all phases of the research.

In phase 1, we will partner with the Los Angeles LGBT Center and include their in-house mentoring program, LifeWorks, as a new component of YM-AIM. The addition of this new component results in a new intervention called Y2Prevent. LifeWorks is a one-on-one mentoring program that fosters personalized matches between LGBTQAI youth aged 12 to 24 years and an adult mentor in their community who can support them with goal setting through 5 achievement areas: home, health, education, career, and personal development [29]. LifeWorks will work together with Y2Prevent staff to enroll Y2Prevent participants in their 12-month mentoring program. Through LifeWorks, participants (mentees) will be matched with a mentor based on the participants' preferences, goals, and overall behaviors. Mentors will then work with the participants to help them map ways to achieve their short-term and long-term goals. LifeWorks staff will remain in contact with Y2Prevent research staff throughout the intervention, document mentor and mentee interactions, and provide monthly updates to Y2Prevent staff for the duration of the intervention. LifeWorks will join Y2Prevent activities during phase 3. Y2Prevent will be introduced by joining 1 session during the phase 3 pilot studies, which will provide the opportunity to introduce the mentorship program directly to the participants. Participants will be expected to sign up for LifeWorks after enrolling in the Y2Prevent pilot phase. Therefore, LifeWorks will enroll participants as they participate in phase 3 of Y2Prevent. Participants will be mentored as they participate in the intervention, which will allow them to discuss their mentoring experience or communicate their concerns to staff. Once the intervention is complete, the Y2Prevent participants may continue to participate in LifeWorks. LifeWorks staff will continue to provide monthly updates to Y2Prevent staff to report on participant engagement with the mentorship program and discuss any barriers and facilitators to engagement or voluntary withdrawal, if applicable.

During phase 2, working groups with African American YMSM will be conducted to assess the acceptability and appropriateness of the mentoring component and to further refine the content of Y2Prevent. These working groups will be used to inform the best strategies to include current approaches to HIV prevention, such as PrEP, PEP, and HIV and STI testing. This will be accomplished by recruiting up to 16 African American YMSM, aged 18 to 24 years, and assigning them to 1 of 2 working groups (each with 6-8 members). Each working group will meet weekly for 7 weeks. During each working group meeting, participants will be presented with preselected topics for that session ranging from relationship building, challenges, and facilitators to HIV prevention and perceptions about PrEP. Working group participants will also be probed for feedback on the mentoring component of the intervention. The working group sessions will be recorded and transcribed, and the feedback provided will be used to tailor the content of the intervention, including the in-session activities and between-session homework assignments, and incorporate new content related to HIV prevention, including information about PrEP and PEP, and HIV testing, as recommended by the CDC. The intervention will be manualized for use during the evaluation, and participants will be provided with a meal and compensated US $40 per working group session—a total of up to US $280 for attending all 7 weekly sessions.

For phase 3, we will incorporate findings from the phase 2 working groups and further refine Y2Prevent to reflect the expectations and motivators of African American YMSM. We will then pilot test Y2Prevent for its feasibility, acceptability, and preliminary efficacy. Specifically, we will conduct formative research with 30 African American YMSM through 3 pilot groups to test and refine the Y2Prevent assessment measures (see the Measures section) to ensure that questions asked to participants are relevant, important, and reflect their everyday lived experiences. To do this, participants will meet once per week for 7 weeks, participate in the revised intervention as informed by phase 2, and provide feedback about their overall experience, including recruitment, their experience with the sessions, and their perceptions of the session content. Participants will be provided with a meal and compensated US $50 for each session they attend, or a total of US $350 for attending all 7 sessions.

Community Advisory Board

A community advisory board (CAB) and youth advisory board (YAB) were established for this study. Both the CAB and YAB will advise study implementation, starting from recruitment, to retention, and refinement of the intervention and assessment measures. The CAB and YAB will be instrumental in interpreting the study findings and disseminating research insights to community partners and stakeholders. The CAB includes policy makers, HIV and AIDS service providers, community advocates, club promoters; the YAB includes members of our target population—African American YMSM. During meetings, Y2Prevent research team members will disseminate findings from the intervention to CAB and YAB members and together brainstorm ideas to best continue tailoring the intervention and strategies to disseminate research findings. The YAB will convene monthly, whereas the CAB will convene quarterly, and will be informed of advancements during all 3 phases of Y2Prevent. To date, the CAB and YAB have assisted in individuating relevant psychosocial assessments for participants and in identifying recruitment strategies and locations to recruit participants.

Study Participants and Recruitment

Young men will be eligible to participate in phases 2 and 3 of research if they meet the following criteria: (1) age between 18 and 24 years; (2) self-identify as male; (3) self-identify as Black or African American; (4) self-identify as gay, bisexual, or other same-sex identity and report having sex with men; (5) report a negative HIV status; (6) are not currently enrolled in another HIV prevention program; and (7) live in Los Angeles County.

Participants will be recruited using social media platforms including Grindr, Twitter, and Instagram. If eligible, youth will be contacted by a member of the research team who will discuss the intervention and requirements of participation in the study. Informed consent will be obtained via an internet-based signature service —that is, DocuSign Inc software.

Tracking and Retention

A tracking protocol developed for longitudinal research with African American YMSM [30] was used to maintain contact with the study participants. This protocol involves collecting and maintaining current contact information from participants, including addresses, emails, phone numbers, and social media handles. The research staff will contact the participants once a month to maintain current contact information. Participants will receive a US $5 incentive for their monthly check-in with research staff.

During phase 3, Y2Prevent will be pilot tested with 30 African American YMSM in 3 groups, each with up to 10 participants. All participants will be screened for eligibility and, if eligible, will be presented with the study description, asked to provide informed consent, and complete a baseline assessment. Pilot group participants will also be informed that their participation and feedback will determine the appropriateness of the intervention for African American YMSM and will be used to further develop and refine Y2Prevent. Participants will receive up to US $570 for participating in all components of the Y2Prevent pilot group, which includes 7 group sessions, 4 data collection periods including HIV and STI and substance use screens, the LifeWorks mentoring component, and monthly check-ins.

The pilot groups will be executed in sequential order so that the experiences from the first group can be used to adapt and further refine the intervention before it is pilot tested with the second group. Feedback from the first group will be used to adapt and refine the intervention for the second group, and feedback from the second group will be used to further adjust the intervention and test with a third pilot group. All pilot group sessions will last from 1.5 to 2 hours and will be held weekly for 7 consecutive weeks. A process evaluation will be performed throughout the pilot groups to document these experiences and to identify barriers and facilitators with respect to implementing Y2Prevent with our target group.

Measures

Evaluation of the intervention's primary outcomes will involve administering a web-based self-report survey to participants at 4 time points: at baseline; after the intervention; and at 3 months and 6 months following completion of the intervention. The survey was administered via the internet using Qualtrics XM software. Evaluation of the acceptability and feasibility of Y2Prevent will be assessed through individual session satisfaction surveys administered immediately after each session and through an exit interview that will take place upon completion of Y2Prevent.

Primary Outcome Variables

Alcohol and illicit drug use will be assessed using scales from the monitoring the future study**,** including lifetime, past 6 months, and past 30 days of illicit drug and alcohol use (past 1 and 3 months, and number of days in the last month) [31]. Participants will be asked about their use of marijuana, lysergic acid diethylamide, phencyclidine, mushrooms, cocaine, crack, ecstasy, stimulants, and prescription drugs without a physician's prescription. Participants will be asked about the circumstances during which they use substances; for example, larger parties versus more intimate gatherings. We will also collect urine samples at baseline, after the intervention, and at 3 months and 6 months after the intervention to test for metabolites of methamphetamines, cocaine, ecstasy, marijuana, and opiates using the Integrated E-Z Split Key Cup II—5 Panel (Innovacon Laboratories), which can detect drugs from 1 to 4 days after use, except for chronic marijuana use, which can be detected for up to 30 days [32].

Sexual risk behaviors, partners and HIV risk, and protective behaviors will be assessed using scales adapted from the Healthy Young Men's (HYM) Cohort Study [4,30]. Participants will be asked about their lifetime and recent sexual experiences (past 1 and 3 months), including insertive or receptive oral sex, insertive or receptive vaginal sex, and insertive or receptive anal sex. Specifically, participants will be asked to report the number of times they engaged in each type of sexual activity and the gender and sexual orientation of their partners. They will be asked about their sexual activity for different partner types (eg, primary, consistent casual, and casual) that they might have had in the past 3 months. They will be asked about the

frequency of condom use and about their most frequent sexual activities. Finally, participants will be asked if they had ever and recently (past 1 and 3 months) exchanged sex for money, drugs, food, clothes, or other necessities. Condom use behaviors will be assessed by the Condom Use Self-Efficacy Scale: the 15-item Condom Use Self-Efficacy Scale measures condom use self-efficacy using a 5-point Likert scale.

HIV and STI testing and prevention behaviors and HIV status will be assessed using existing scales developed for use with African American YMSM [30], including participants' self-reported HIV testing history and self-reported HIV status [4,30]. We will test for HIV using the INSTI HIV-1 or HIV 2 antibody test.

Participants will be asked to undergo a rapid test for HIV at baseline and 6-month follow-up assessments; participants with preliminary positive results will be referred to a confirmatory test, and those who seroconvert will be linked to HIV care. Participants will also self-collect rectal specimens for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* nucleic acid amplification testing (Hologic) at baseline and at the 6-month follow-up. To ensure a smooth linkage to the care process, those with positive results will be referred and treated at a clinical partner site according to the CDC and Los Angeles County guidelines. Furthermore, we will use scales developed in prior research to assess knowledge and attitudes about PrEP and PEP and to measure adherence to PrEP for those reporting its use [33].

Potential Mediator or Moderator Variables

Demographic

The modified HYM Study [4,30] screening and survey instruments will obtain demographic information, including age, race or ethnicity, residential stability, education or employment, and insurance status.

Social Ecology of Youth: Positive Self-concept

The 15-item Multigroup Ethnic Identity Measure [34], used in dozens of studies with consistently high reliability (Cronbach α=.80), measures ethnic identity search and affirmation, belonging, and commitment. Sexual Self-Concept is a multidimensional construct that refers to one's positive and negative feelings about their sexual being. This will be measured using the Multidimensional Sexual Self-Concept Questionnaire, a 20-item scale that has been validated with multiple populations of adolescents [35].

Social Support

To measure perceived support from family, friends, and intimate partners, we will use the Multidimensional Scale of Perceived Social Support, a 12-item scale used in the HYM Study [36].

Health, Depression, and Well-being

Health, depression, and well-being will be assessed at pre, post, and 3- and 6-month follow-ups. The 18-item Brief Symptom Inventory will be used to assess depression, anxiety, and somatization [37]. Furthermore, we will use the Adult Mental Health Continuum—Short Form, a 14-item assessment that measures emotional, psychological, and social well-being [38]. The short form has shown excellent internal consistency (>0.80) and validity in adolescents and adults in the United States, the Netherlands, and South Africa.

Resilience will be assessed using the Brief Resilience Scale, which assesses the ability to bounce back [39].

Process Evaluation

Overview

We will use process evaluation techniques to evaluate the adoption, acceptability, satisfaction, and intervention dosage during phase 3 of the study. The process evaluation will document (1) fidelity to the adapted intervention, (2) experiences of the participants to ensure the intervention's appropriateness and cultural relevance, and (3) experiences of the facilitators to inform future implementation in clinical and community settings. The quality of the intervention will be assessed through a modified version of the Fidelity of Implementation Rating System, which scores the quality of delivery of individual intervention components [40]. Observations, session notes, and structured exit interviews will be used to document and analyze the implementation of Y2Prevent.

The research team will conduct observations and audio-record Y2Prevent group sessions. These recordings will be transcribed and analyzed by the research team to assess fidelity to the intervention, level of engagement by the participants, and the extent to which outside influences may interfere with session activities. Multiple team members will review and code session observations to ensure interrater reliability [41]. Qualitative exit interviews of 20 to 30 minutes will be conducted with each participant and his identified mentor (separately) at the end of the Y2Prevent piloting to document individuals' impressions of the Y2Prevent and control conditions. The open-ended questions will focus on motivations for participation, extent to which expectations were met, reasons for continuing to attend sessions, overall impressions, how they will incorporate what they learned from Y2Prevent into their lives, favorite or least favorite aspects, and any additional desired features or content. Individuals who drop out of the program will be contacted to assess their experiences and reasons for not attending. Interviews will be analyzed by diverse members of the research team, with a focus on understanding how to maximize the acceptability and feasibility of the intervention. An issue log will be maintained throughout the pilot.

All exit interviews, notes, observation forms, and intervention staff notes will be transcribed as required and entered into a single database. Using the same analytic approach as described previously, the process evaluation will focus on the following: (1) reasons for participation or nonparticipation, (2) program modifications (eg, length, schedule, and facilitation issues), (3) perceived benefits of participation, and (4) components of Y2Prevent that require modifications. At the end of each of the 3 pilot sessions, the evaluator will provide a summary of the preliminary evaluation results and share it with a larger team for review to identify modifications to the intervention as needed. For example, if after the pilot session, participants report that engaging with an assigned mentor through LifeWorks was a challenge. We will include additional information in the

sessions on how to refine and improve the matching process based on the participant feedback.

Process measures include data on the sources of recruitment and recruitment rates, trial retention rates, and identification of barriers to and facilitators for recruitment and retention. Notably, the process evaluation will appraise the internet-based nature of the intervention; questions in the survey administered at the end of each session and in the qualitative exit interview will gather insight into participant experiences and overall satisfaction with the internet-based format.

Exposure to Other HIV Interventions

We will assess exposure to other HIV prevention information from sources such as television or radio, social media, friends, and other interventions using a short survey at the end of each weekly session.

Satisfaction

A brief satisfaction assessment (3-5 questions) will be administered at the end of each Y2Prevent session. This assessment will identify the most and least helpful aspects of the session, information or content missing from the session, satisfaction with activities and exercises, etc. This assessment will be used to provide real-time participant feedback.

Data Analysis Plan

The pilot study will include 30 participants who will participate in 4 assessments (before the intervention, after the intervention and 3 and 6 months after the conclusion of the intervention). Data related to feasibility, acceptability, and adherence will be summarized as means and proportions with 95% CIs by the assessment period. Pre- to postintervention changes at different intervals will be evaluated using generalized linear mixed models; a subject-level random intercept will be specified. Estimates of changes at each postintervention assessment will be calculated, along with 95% CIs. Data will be summarized to identify any systematic differences in pilot outcomes to inform future large-scale randomized clinical trials. Furthermore, qualitative data from the exit interviews will be thematically assessed for positive or negative sentiments regarding participation in Y2Prevent.

Procedures for cleaning and screening data will include identifying and rectifying missing data and logical errors. Descriptive analyses will consist of univariate analyses, including SD, range, and value; patterns of correlation and covariance checks for multicollinearity; and identification of outliers and data distributions. Variables will be transformed as needed to reduce the effects of valid outliers or violations of normality.

Results

As of June 2022, we have completed phase 1 of the Y2Prevent intervention and initiated our partnership with LifeWorks. We have launched phase 2 of Y2Prevent and have begun recruitment of working group participants. Phase 3 of Y2Prevent is anticipated to be launched in September and is expected to be completed by the end of this project period in December 2022.

Discussion

Study Implications

This study describes the development of an intervention designed to address the specific and intersecting factors that contribute to negative health outcomes among African American YMSM. We discuss the design of the research protocol consisting of 3 phases and the processes followed to use a community-informed and evidence-based approach to design an intervention that is specific to the needs of African American YMSM. Interventions designed to help LGBTQAI youth identify and develop the necessary skills to navigate the social and structural factors that affect their engagement in health promotion activities are scant. Y2Prevent aims to promote African American YMSM's adoption and maintenance of HIV-protective behaviors (eg, safer sex, PrEP use, HIV and STI testing, and health care use).

Limitations and Challenges

There are a few potential challenges we are prepared to address. First, the engagement and retention of African American YMSM in the proposed formative research is a potential challenge. However, we successfully used the same recruitment and retention strategy for YM-AIM and achieved a 100% retention accuracy. Similarly, to address retention throughout the postassessment period, we will use the same retention protocols used in other studies focused on YMSM [30].

Limitations of Y2Prevent include the future generalizability of these results. Owing to our small sample size, our findings cannot be interpreted as representative of African American YMSM who are aged between 18 and 24 years. Second, our mentoring component is housed in a very well-resourced LGBTQ center, which might not be replicable in nonmetropolitan areas.

Conclusions

As the incidence of HIV among African American YMSM continues to increase, innovative interventions such as those using mobile devices to mentor LGBTQAI youth and those who use a holistic approach to HIV prevention will be essential [42,43]. Early engagement with prevention interventions may also promote youth's adoption and maintenance of protective behaviors, such as engaging in safer sex, using PrEP, increasing their HIV and STI testing, and accessing and using health care. Few youth-focused interventions have sought to help youth identify and develop the skills needed to successfully navigate these broader social and structural ecosystems that contribute to individual-level engagement in prevention among sexual minority youth. Therefore, once Y2Prevent is demonstrated to be relevant, feasible, and acceptable, we will conduct a future large-scale efficacy trial.

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Data Availability

Data sharing is not applicable to this study, as no data sets were gathered or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
CDC: Centers for Disease Control and Prevention
EBI: evidence-based intervention
HYM: Healthy Young Men
LGBTQAI: lesbian, gay, bisexual, transgender, queer (or questioning), asexual (or allied), and intersex
PEP: postexposure prophylaxis
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
YAB: youth advisory board
YM-AIM: Young Men's Adult Identity Monitoring
YMSM: young men who have sex with men

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Protocol

Effectiveness of Neurodynamic Interventions in Patients With Stroke: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Stroke is the most common and serious neurological condition, which can lead to death, limited functionality, and reduced quality of life. Studies with conflicting results and various methodological limitations have been conducted to assess the effectiveness of neurodynamic interventions for patients with stroke.

Objective: This systematic review and meta-analysis aimed to investigate the pooled effectiveness of different neurodynamic interventions on patients with stroke.

Methods: The PubMed, PEDro, and Google Scholar databases will be searched for studies published with full text in the English language from inception to date. Randomized controlled trials evaluating the effect of different neurodynamic techniques on patients with stroke will be included. The primary outcome measures will include pain, disability/function, and quality of life. Secondary outcome measures will include physical performance measures such as balance, range of motion, muscle strength, and specific diagnostic and neurodynamic test outcomes. The screening, data extraction, and methodological quality assessment will be performed by two independent reviewers. The PEDro scale will be used to systematically appraise the methodological quality. Review Manager V.5.4 software will be used for statistical analysis. Weighted mean difference or standardized mean difference with 95% CIs and *P* values will be used to calculate the treatment effect for each outcome variable.

Results: Search terms and search databases have been identified. The data extraction sheet has also been developed. This study is expected to be completed by the end of 2022.

Conclusions: This study will provide up-to-date evidence on the effectiveness and use of neurodynamic interventions for patients with stroke in clinical practice.

Trial Registration: PROSPERO CRD42022319972; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=319972

International Registered Report Identifier (IRRID): PRR1-10.2196/38956

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KEYWORDS

stroke; neurodynamic; neurological; physiotherapy; physiotherapist; neural mobilization; review; intervention; search strategy; search strategies; library science; information science; librarian; pain; quality of life; disability; disabilities; physical function

Introduction

According to the World Health Organization, stroke is a condition with no apparent cause other than vascular origin with symptoms lasting for more than 24 hours or leading to death with a rapidly developing clinical sign of focal or global disturbances of cerebral function [1]. Stroke is the most common serious neurological disorder, and in high-income countries, it is the fourth-leading cause of death, long-term disability, and reduced quality of life among adults [1,2]. According to the

American Stroke Association, about 87% of the cases are ischemic, and the remaining 13% are hemorrhagic [1]. The most common symptoms include paralysis (in one or both sides), loss of balance, and spasticity, which commonly appear days or weeks after the occurrence of a stroke [3]. Hemiplegia is the primary motor manifestation of stroke, which is weakness of one half of the body contralateral to the site of a cerebral lesion [4].

Several manual therapy techniques were used in the management of patients with stroke including neurodynamic or neural mobilization (NM) techniques. NM is defined as manual techniques or exercise interventions aimed at affecting the neural structures or surrounding tissue (interface) directly or indirectly with the purpose of reducing pain, decreasing neural tension, and improving muscle flexibility and endurance [2,5]. Studies revealed that NM improves the elasticity of nervous and musculoskeletal tissues, increases the intraneural blood flow, improves intraneural fluid dispersion, reduces intraneural edema, reduces thermal and mechanical hyperalgesia, and reverses the increased immune responses following a nerve injury [2,3,5]. NMs restore the mechanical and neurophysiological function of the nerve and can be performed in different ways using active or passive movement, manual mobilization of the nerve or interface, and exercise [6,7].

A systematic review of the literature on the therapeutic efficacy of NM on various musculoskeletal conditions included 10 randomized controlled trials (RCTs) and revealed that there is limited evidence to support the use of NMs [8]. A systematic review of 13 clinical trials focused on carpal tunnel syndrome concluded that the efficacy of NM for carpal tunnel syndrome was unclear [9]. Another review of 20 clinically controlled trials assessed the effect of NM on chronic conditions and concluded that NM is not superior to other interventions [10]. A study conducted to examine the effect of rhythmic upper extremity neurodynamic for 18 patients with hemiplegia caused by stroke found that rhythmic neurodynamic was effective for improving the functions of upper extremities [11]. A blinded randomized clinical trial study on effectiveness of NMs performed in 12 volunteers, aged between 20 and 80 years, with a diagnosis of ischemic or hemorrhagic stroke showed positive effects in relation to flexibility, lower limb muscle strength, gait, and balance [2]. A study on 26 patients with stroke undertaken to compare the efficacy of instrument-assisted soft tissue mobilization and a neural dynamic technique on lower extremity muscle tone, stiffness, and static balance showed a significant improvement in the instrument-assisted soft tissue mobilization group in muscle tone and stiffness but no difference in static balance [3]. A quasi-experimental study to determine the effect of the neurodynamic sliding technique on 20 hemiplegic patients with hamstring tightness showed improved hip flexion assessed by the passive straight leg raise test [12]. A case report study on a combination therapy of botulinum toxin type A and NM for a patient with severe upper limb spasticity and pain after stroke showed an improved joint range of motion and decreased pain, anxiety, and depression [7]. A pretest and posttest experimental study on 20 patients with traumatic spinal cord injury (level C5-C8) and upper limb spasticity in the finger and wrist flexors suggest that neurodynamic mobilization of the median nerve may be effective for upper limb spasticity control and upper limb functional improvements [13].

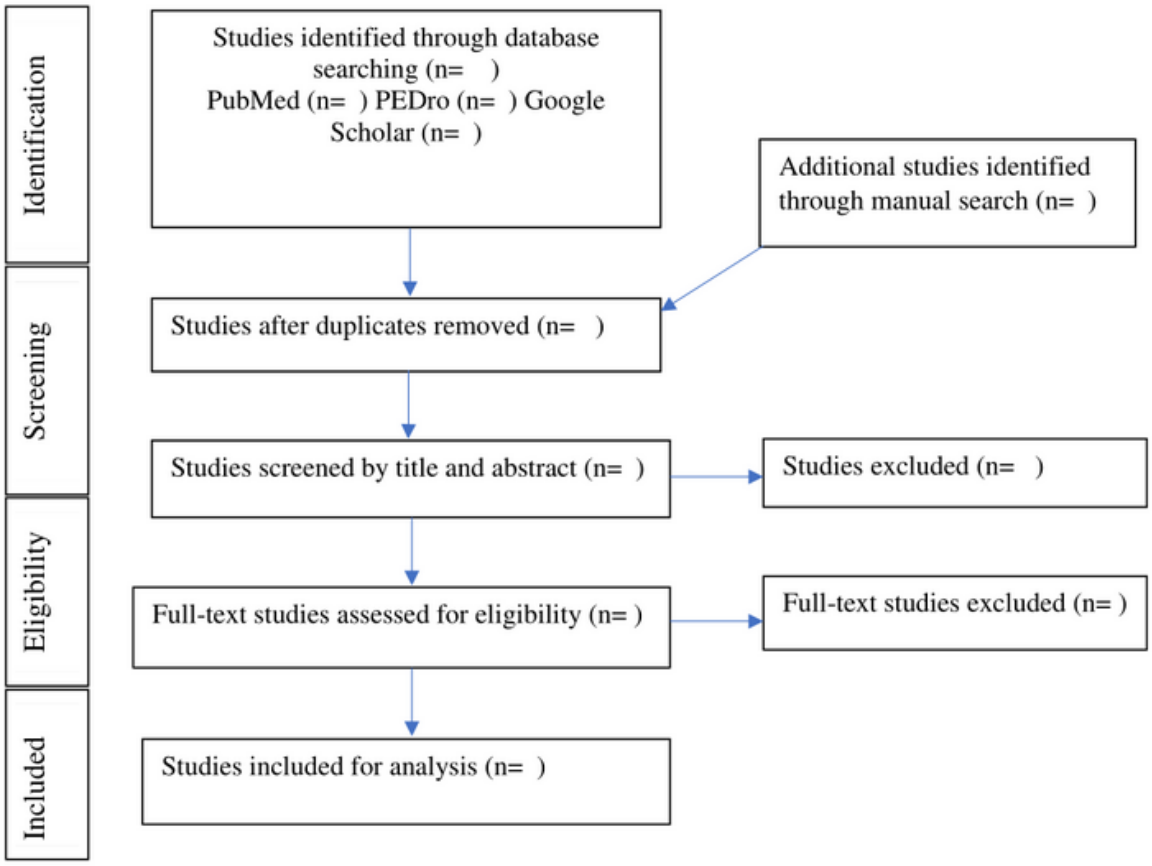
A systematic review on neurodynamic techniques and mobilization in stroke rehabilitation finally included 12 studies (7 were RCTs, 3 quasi-experimental, 1 case report, and 1 systematic analysis) and concluded that there is limited evidence to support the use of NM techniques [4]. Another review on NM as a therapeutic option in the treatment of stroke included only 6 studies, and the results indicated beneficial effects of NM in the control of muscle tone, range of motion, and functionality of patients affected by stroke [14]. Previous studies on NM interventions on patients with stroke were limited to qualitative analysis, were not up to date, and had unclear or conflicting results [4,5,8,14]. Due to the limited evidence and varying methodological quality, conclusions may change over time [5], and new RCTs are available in the literature. For these reasons, we plan to perform this systematic review and meta-analysis to generate new evidence. The aim of this systematic review and meta-analysis is to systematically assess the types and techniques of different neurodynamic interventions used and their effectiveness on pain, disability, functional status, quality of life, and other variables on patients with stroke.

Methods

Overview

This systematic review and meta-analysis protocol is prepared according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [15]. The reporting flowchart is presented in Figure 1. This systematic review is registered on PROSPERO with the registration number CRD42022319972. A preliminary database search and development of a data extraction sheet were undergoing during the submission of this manuscript.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.



Search Strategy

To find both published and unpublished studies, a three-step search strategy will be used. An initial limited search of PubMed will be carried out to find relevant Medical Subject Headings (MeSH) and entry terms. A second search using all identified MeSH and entry terms will then be undertaken across the PubMed, PEDro, and Google Scholar databases. Third, the reference lists of all identified studies will be searched for additional studies and articles published from inception to date. The search terms with multiple combinations will be stroke, cerebrovascular disease, hemiplegia, neural, nerve, mobilization, manipulation, physical therapy, physiotherapy, manual therapy, glide, slide, tension, stretching, neurodynamics, and RCTs. Two reviewers will independently screen the titles and abstracts of the studies, and any disagreement between the reviewers will be resolved by consensus or by a third reviewer. The search strategy of the PubMed database is presented in Table 1.

Table 1. PubMed search strategy.

Search number	Search detail
1	“stroke”[MeSH Terms]
2	“stroke”[Title/Abstract] OR “apoplexy”[Title/Abstract] OR “cerebrovascular accident”[Title/Abstract]) OR “cerebral stroke”[Title/Abstract] OR “cerebrovascular accident”[Title/Abstract] OR “cerebrovascular accident acute”[Title/Abstract] OR “cerebrovascular apoplexy”[Title/Abstract] OR “cerebrovascular stroke”[Title/Abstract] OR “stroke acute”[Title/Abstract] OR “vascular accident brain”[Title/Abstract]
3	“stroke rehabilitation”[Title/Abstract] OR “mobilization”[Title/Abstract] OR “neural dynamic”[Title/Abstract] OR “neurodynamic”[Title/Abstract] OR “neuro dynamic technique”[Title/Abstract] OR “manual therapy”[Title/Abstract] OR “manipulation”[Title/Abstract] OR “physical therapy”[Title/Abstract] OR “physiotherapy”[Title/Abstract] OR “glide”[Title/Abstract] OR “slide”[Title/Abstract] OR “tension”[Title/Abstract] OR “stretching”[Title/Abstract]
4	#1 OR #2
5	#3 AND #4
6	Limit to “randomized controlled trial” OR “clinical trial” OR “controlled clinical trial”

Inclusion Criteria

Types of Participants

This systematic review will consider studies that include human participants older than 18 years affected by stroke.

Types of Interventions

This review considers studies that evaluate neurodynamic interventions performed on patients with stroke. The intervention group (neurodynamic interventions) will be compared to a control group where another or no type of intervention has been performed. NMs are divided into "sliders" and "tensioners." Sliders will elongate the nerve bed through movement at one joint while moving another joint to relieve tension in the nerve. With tensioners, joints are moved in such a way that the nerve bed is elongated and the tension in the nerves increases [6].

Types of Outcomes

This systematic review will consider studies that include the following primary outcome measures: pain (numerical pain rating scale, visual analog scale), disability and function (Disability of the Arm, Shoulder, and Hand Symptom Scale; Neck Disability Index; Roland Morris; Oswestry; Patient Specific Functional Scale), and quality of life (36-Item Short Form Survey, EQ-5D, World Health Organization Quality-of-Life Scale Physical Domain Score). Secondary outcome measures include physical performance measures like balance (Berg Balance Scale), range of motion (inclinometer, goniometer), muscle strength (Oxford grading, dynamometer), sensation (light touch, pinprick, two-point discrimination, thermal pain threshold), specific diagnostic tests (Tinel's sign, Phalen's maneuver), and neurodynamic test outcomes (Upper Limb Neurodynamic Test, straight leg raise, slump, prone knee bend, passive neck flexion).

Types of Studies

RCTs evaluating the effect of neurodynamic interventions on patients with stroke will be included. Studies that included infants and children, studies with a small sample size, and studies that do not have enough statistical information to be extracted will be excluded. Studies not published in English will be excluded.

Data Extraction

Data will be extracted independently by two reviewers using a standardized data extraction tool. The data extracted will include specific details about the study methods, populations, interventions, and outcomes of significance to the review question. The data extraction sheet is presented as Multimedia Appendix 1. Authors will check for completeness and any disagreements will be resolved by discussion.

Methodological Quality Assessment

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using the PEDro scale [16]. The possible score on the scale ranges from 0 to 10, with a higher score indicating a higher quality of methods used in the study. A study with a score of 6 or more is considered as evidence level 1 and will be included for data extraction [17]. Any disagreements that arise between the reviewers' scores will be resolved through discussion or with a third reviewer.

Statistical Analyses

Review Manager V.5.4 (Cochrane Collaboration) software will be used to analyze the statistical data. We will calculate the treatment effect size as weighted mean difference or standardized mean difference with a 95% CI, and results will be displayed in the form of forest plots. Heterogeneity among included studies will be assessed using the I^2 test. If I^2>0.5 or P<.10, the study is considered to have a significant heterogeneity among the included studies, [18] and a random-effect model will be used in this case. Where statistical pooling is not possible, the findings will be presented in a narrative form, including tables and figures to aid in data presentation where appropriate.

Ethical Considerations

Ethical approval and informed consent are not required, as this study is a literature review that only involves the use of previously published data and does not include any patients.

Results

The search terms and databases have been identified. After selecting relevant studies and assessing the methodological quality, data extraction and statistical analyses will start. The data synthesis and presentation of the findings will be completed by the end of 2022. The final results will be published in a peer-reviewed journal and will be presented at relevant conferences and events.

Discussion

This systematic review and meta-analysis will analyze the effects of different neurodynamic interventions on patients with stroke. We will explore their effect on pain, disability/functional status, quality of life, and other variables where data are available. We will also explore the types/techniques and durations of the interventions used. The final results will bring new and up-to-date evidence by investigating the pooled effect of neurodynamic interventions on patients with stroke in the literature. However, this study will have several potential limitations. First, a lack of RCTs with an adequate sample size might be the primary limitation. Second, there may be substantial heterogeneity due to the quality of different studies and due to different methods of neurodynamic interventions (eg, passive vs active approach, sliding vs tensioning techniques, and global vs local tissue mobilization). Finally, some RCTs may be of poor quality, and there may be a potential risk of bias. The final results of this systematic review and meta-analysis will be published in a peer-reviewed journal and presented at relevant conferences and events.

Authors' Contributions

AAS conceptualized the research question, wrote the first draft, designed the search strategy, and edited and approved the final version of the manuscript. AHM edited the first draft, revised the search strategy of databases, developed the data extraction form, and edited and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction sheet (sample).
[DOCX File , 14 KB - resprot_v11i9e38956_app1.docx]

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Abbreviations

MeSH: Medical Subject Headings
NM: neural mobilization
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial

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Protocol

Determinants of Physical Activity in the Cardiac Population: Protocol for a Systematic Review

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Abstract

Background: Lack of physical activity is a critical contributing risk factor to cardiovascular disease. Hence, regular physical activity is a mainstay in the primary and secondary prevention of cardiovascular disease. Despite the extensive promotion of physical activity in both primary and secondary prevention programs, including cardiac rehabilitation, physical activity levels in the cardiac population remain low. Therefore, it is crucial to understand critical determinants that influence physical activity behavior.

Objective: This study aims to deliver a systematic review of studies with collated observational data exploring the association between determinants and physical activity behavior in the target population. These new insights inform the design of future interventions targeted at lasting heart-healthy physical activity behavior in the cardiac population.

Methods: Primary studies with observational quantitative data on determinants and their association with physical activity behavior in the cardiac population will be included. Information on relevant primary studies will be retrieved from various databases, including Embase, CINAHL, MEDLINE, PsycInfo, and Web of Science Core Collection. Six reviewers will independently double-screen articles. Studies will be selected according to the prespecified inclusion and exclusion criteria. Data will be extracted and entered into suitable worksheets. The US-based National Heart, Lung, and Blood Institute's Study Quality Assessment Tool for Observational Studies will be used to assess the quality of all eligible primary studies. The results will be presented in a descriptive and narrative synthesis. If the type and quality of data are suitable, meta-analyses will be conducted. Study reporting will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Results: Data collection started in September 2020, and the literature search was updated in July 2021. Data synthesis is ongoing, and the literature search will be updated in October 2022.

Conclusions: This review will be valuable to relevant stakeholders, including clinicians and health care professionals, intervention developers, and decision makers in health care. It lays a comprehensive foundation for understanding the determinants of physical activity to inform the design of secondary prevention interventions relevant to the cardiac population.

Trial Registration: PROSPERO CRD42020206637; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=206637

International Registered Report Identifier (IRRID): RR1-10.2196/39188

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KEYWORDS

behavior change; cardiac rehabilitation; cardiovascular disease; determinants; heart healthy; physical activity; protocol; secondary prevention; systematic review; cardiac disease; heart disease; clinician; health care worker; health intervention; decision-making; health promotion

Introduction

Background

Cardiovascular disease (CVD) is the number one cause of death and disability worldwide, taking approximately 17.9 million lives each year [1]. The pre-eminence of cardiac events has not substantially changed over the past three decades [2]. This applies especially to the population older than 60 years. Numerous modifiable risk factors associated with an unhealthy lifestyle contribute to CVD, such as diabetes, hyperlipidemia, arterial hypertension, obesity, smoking, and physical inactivity. In a recent large-scale epidemiological study of over 155,000 participants across 21 high-, middle-, and low-income countries, it was estimated that 70% of CVD cases and deaths in the overall study population could be attributed to modifiable risk factors [3]. Although physical inactivity is one of the most deleterious cardiovascular risk factors, which co-influences other heart-critical risk factors such as dyslipidemia, diabetes mellitus type 2, obesity, and arterial hypertension, levels of physical activity remain well below current recommendations [4,5].

The current World Health Organization recommendations call for 150 to 300 minutes of moderate-intensity physical activity, 75 to 150 minutes of vigorous-intensity physical activity, or a combination of both for healthy adults per week. These recommendations are also a target for cardiac rehabilitation; nonetheless, a study surveying 8261 coronary patients from 27 European countries between 6 and 24 months after a cardiac event found that only 35% of respondents reported that they were performing planned physical activity to increase physical fitness, while 42% reported that they were not performing any planned physical activity and that they had no intention to do so [6].

In secondary prevention, cardiac rehabilitation programs promote physical activity for people with CVD. The concept of cardiac rehabilitation refers to interventions targeted at mitigating the effects of underlying heart conditions and restoring physiological, psychological, and societal functioning, reducing the overall risk of morbidity and mortality [7,8]. Although research on exercise-based cardiac rehabilitation offers good evidence of its positive effects on the physical and mental health of people with cardiovascular conditions, challenges remain in maintaining physical activity behavior after completing cardiac rehabilitation [9].

Reasons for nonmaintenance are multifactorial. Previous studies suggest that several determinants influence physical activity behavior in the cardiac population, namely, health beliefs [10-12], illness cognition [13-15], health literacy [16,17], sociodemographics [18,19], and health conditions and comorbidities [20-22]. While there have been individual observational studies and randomized controlled trials that have captured quantitative data on determinants of physical activity in the CVD population, to our knowledge to date, there have not been any systematic reviews and meta-analyses of these quantified associations between determinants and physical activity behavior. There is, therefore, an opportunity for the systematic collection and analysis of this body of data using a systematic review study design, providing collated insights into the determinants of physical activity and the strength of their associations with physical activity in this population.

Rationale

No existing systematic and comprehensive collation and appraisal of the available data on the quantified association of different determinants with physical activity behavior in the cardiac population could be identified. It is expected that such findings may allow for a comparison of the relative importance of determinants for heart-healthy physical activity levels in people with CVD. (The lay term *heart-healthy* in this context is chosen deliberately to convey that the physical activity is intended to contribute to maintaining or improving cardiovascular health.) These findings can inform research and interventions concerned with health behavior change by shedding new light on how determinants operate within specific sociodemographic, social-cognitive, health-related, and physical environmental contexts.

Objectives

The objectives of this systematic review are to:

- Identify relevant determinants of physical activity behavior in the cardiac population
- Determine the strength of the association between the identified determinants and physical activity behavior

Methods

Overview

This systematic review protocol specifies the conduct and reporting of a systematic review in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. This protocol follows the 2015 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [23] (Multimedia Appendix 1). This systematic review will include studies that provide observational data quantifying the association between determinants and the outcome of interest (ie, physical activity–related behavior) such as odds ratios, correlation coefficients, and multivariate regression coefficients. This could include studies with cross-sectional or longitudinal observational designs or secondary analyses of experimental studies (eg, analysis of data from a *usual care* control group). This protocol has been registered with PROSPERO (registration CRD42020206637).

Eligibility Criteria

Search Domains

The search domains consist of population, determinants of physical activity, and outcome behavior (physical activity).

Study Populations

This systematic review focuses on ongoing self-initiated heart-healthy physical activity behavior of the adult cardiac population. The study population is defined as adults (aged ≥18 years) who fulfill the medical indications for cardiac rehabilitation. The reason for defining this population description is that a medical indication for cardiac rehabilitation

implies an evidence-based recommendation for the person to carry out ongoing heart-healthy physical activity and exercise as part of their individual lifelong secondary CVD risk prevention.

The specific medical indications for cardiac rehabilitation vary between countries but commonly include, among others [4,24,25]:

- Acute coronary syndrome, including ST-elevation myocardial infarction and non–ST-elevation myocardial infarction
- Bypass surgery
- Other heart surgeries
- Heart and lung transplantation
- Chronic heart failure
- Percutaneous coronary intervention
- Chronic coronary heart disease
- Pulmonary hypertension
- Condition after an electrophysiological intervention
- Cardiac pacemaker or a defibrillator
- Hemodynamically stable arrhythmia

Determinants

Determinants (ie, factors that are associated with physical activity behavior) include socioeconomic, environmental, and psychological factors, as well as personal characteristics and demographics. The domain *determinants* includes search terms such as determinants, factors, influences, barriers, obstacles, facilitators, mediators, enablers, causes, reasons, triggers, contributors, predictors, and correlates. This systematic review will include both modifiable (eg, psychological factors) and nonmodifiable determinants (eg, demographics). However, the focus will lie on potentially modifiable determinants that are amenable to change, as the findings from this review should ideally inform future intervention designs to address these determinants. Examples for expected determinants under each determinant category are age, gender, and marital status in the demographics category; anxiety, depression, and kinesiophobia in the psychological factors category; self-efficacy, subjective norm, and illness perception in the cognitive factors category; and severity of cardiac condition and level of comorbidity in the morbidity category.

Outcome Behavior

Relevant for this systematic review will be any outcome that demonstrates physical activity behavior. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure at work or during leisure time such as sports, conditioning exercises, household tasks, and other activities [26]. Both self-reported and tracked physical activity data will be included. *Self-reported* physical activity data refers to information provided by self-completion of a questionnaire or by answering questions posed by a researcher or health care professional. *Tracked* refers to physical activity data that is collected through sensor devices, including consumer-grade devices (smartphones, smartwatches, pedometers, wearable activity trackers such as Fitbit) and research-grade sensors (inertial measurement units, accelerometers).

Different outcome measures will be considered, including measures describing the level of physical activity (eg, daily/weekly minutes of moderate and vigorous physical activity, step count, energy expenditure, and instrument-specific activity scores or categorization to activity levels) as well as descriptions of adherence to physical activity recommendations (eg, adherence to the World Health Organization physical activity recommendations).

Descriptions of dynamic subbehaviors (change) of physical activity over time (starting, stopping, increasing, reducing, and switching the type of activity, sport, or exercise) will be included, with the intention to identify determinants of change dynamics. More differentiated aspects of physical activity behavior over time are:

- Maintaining/sustaining
- Starting/beginning
- Changing frequency/intensity/time (duration)/type of physical activity (Frequency, Intensity, Time, and Type principle [27])
- Stopping/discontinuing

Explicitly excluded will be outcomes describing attendance at or completion of cardiac rehabilitation exercise programs and outcomes describing adherence to professionally guided home- or community-based exercise training interventions for people with CVD. Because these types of programs are generally highly resourced and time-limited, these outcomes are considered less helpful toward the aim of this review, which concerns ongoing self-initiated heart-healthy physical activity behavior.

Additional Criteria

This review includes publications in which precise association statistics such as odds ratios and correlation coefficients are presented. Publications that report on associations between determinants and outcome behavior without presenting precise association statistics will be excluded.

This review includes journal publications in English, Dutch, and German. To be able to apprehend state-of-the-art literature, the search includes journal publications from the past 15 years (2005-2020). Peer-reviewed literature only will be included to address the objectives specified above.

Information Sources

Studies will be retrieved using five bibliographic databases, namely, MEDLINE via PubMed, Embase, Web of Science Core Collection, PsycINFO, and CINAHL. Preliminary searches of PROSPERO and the Cochrane Database of Systematic Reviews were performed to confirm that no systematic review with a similar research scope has previously been conducted or is currently underway, ensuring that this study delivers relevant and novel insights.

Search Strategy

A scoping literature search of PubMed was performed by one researcher (STK) to identify which descriptors authors use for the population, determinants, and outcome behavior targeted by this study. From this, a detailed search strategy was developed for each electronic database by three researchers (JG,

STK, RC) and an experienced librarian from Maastricht University Library to identify studies for inclusion. The complete search strategies for all bibliographic databases are provided in Multimedia Appendix 2. To reach a high level of methodological transparency and reproducibility, the search strategy will be piloted by two researchers (JG, STK) independently. The search strategy will be used for the identification of study records in relevant electronic databases.

The search strategy contains terms that refer to determinants and contributors associated with physical activity in cardiac rehabilitation and secondary prevention in people with cardiac disease; these terms will be adapted for use in all databases. The search strategy includes the main sets of keywords referring to "determinants," "physical activity," and "cardiac rehabilitation".

The search terms were combined using the Boolean operators "AND" and "OR." Subsequently, a search strategy was developed by combining Medical Subject Headings (MeSH) terms and word searches in the title or abstract. Publications were filtered by publication year range and human studies; no other filters were applied. The search strategy for the systematic review will be documented in a table stating the database, the date, the search terms, the database fields, and the number of search results.

Data Management

Search results will be imported into the reference manager software EndNote (Clarivate). This facilitates systematic and comprehensive data management by storing, organizing, and merging duplicates of scholarly articles in one application. Titles and abstracts will then be transferred to a Google Sheet. The Google Sheet includes two worksheets. The first worksheet contains a queue with the inclusion criteria, drop-down menus, and a designed data-screening algorithm. When the screener chooses "No" in the drop-down function for any of the inclusion criteria, the final screening decision cell will automatically indicate "exclude"; if "unsure", it switches to "?"; and if all inclusion criteria are fulfilled and can be answered with "Yes," the final screening decision column automatically indicates "include." The second working sheet consists of the working definitions for the three search domains "population," "determinants," and "outcome behaviour." This Google Sheet design is intended to support and manage a larger group of reviewers by creating an efficient and convenient workflow for screening and data extraction, and to ensure that screening decisions and data extractions are documented and auditable.

Study Selection Process

This review will include primary research studies only. The screening of records will be performed against the eligibility criteria. Disagreements between reviewers regarding screening decisions will be resolved by consensus or by a third independent reviewer's decision.

The first phase of the study selection process consists of screening by title and abstract according to predefined dimensions: population, determinants, and outcome behavior. In phase two, the team will screen the full texts of documents to verify the studies' eligibility. At each phase, independent double-screening will be conducted by a team of up to 8 reviewers. Discrepancies in screening decisions will be resolved by discussion, with the involvement of a third reviewer where necessary.

A flowchart following the PRISMA statement [23] will be created to document the selection process. The flowchart includes the search results, the removed primary studies after reviewing the title or abstract, the citations obtained in full text, the removed studies after full-text screening including duplicated records and irrelevant studies, and the ultimately included primary studies.

Data Extraction

Data will be extracted by record number and include all relevant information: article ID, author, journal, study title, language, year of publication, study aim, study design, sample description (characteristics and size), setting and country, determinants, methods of assessing determinants, type of outcome, outcome assessment methods, types of effect sizes calculated for associations between determinants and outcome (odds ratios, correlation coefficients, multivariate regression coefficients), and reported effect sizes for association statistics with measures of precision (CIs, R^2 values) and summary statistics for determinants and outcome parameters (frequencies, measures of central tendency, and spread). If associations have been reported for subgroups of the study sample, sample sizes of subsamples will be noted.

Quality Assessment

To assess the methodological quality of included studies, the research team will use the US-based National Heart, Lung, and Blood Institute's Study Quality Assessment Tool for Observational Studies [28]. This tool is suitable as it matches the chosen study designs and the level of detail required in the assessment, and it guides and enables the process of differentiating between internal validity (risk of bias) and external validity (generalizability). The quality of the individual studies will be assessed independently by two reviewers; disagreements will be resolved by discussion, and if necessary, a third reviewer will be consulted.

Data Synthesis

An initial descriptive synthesis will be conducted using text and tables, including a summary of included studies, quality assessment, and a description of the risk of bias for individual studies. After that, a narrative synthesis will be conducted. The strength of associations between identified determinants and physical activity behavior will be assessed and described according to qualitative descriptors proposed by Rosenthal [29].

If the data is suitable, a quantitative synthesis (meta-analysis of effect sizes regarding determinants of physical activity) will be performed. Heterogeneity will be assessed using the I^2 statistic and sensitivity analyses by comparison of subgroups stratified by clinical characteristics, outcome parameters, and study designs. The degree of heterogeneity observed will inform the decision to proceed to a meta-analysis and the choice of fixed-effects model (in case of homogeneous data) or random-effects model (in case of heterogeneous data). A forest

plot will be constructed to graphically illustrate the meta-analysis. The possibility of publication bias will be examined using a funnel plot [30].

Depending on the types and numbers of primary studies identified, analyses of subsets may be performed as well, for example, according to a specific physical activity behavior such as stopping physical activity after cardiac rehabilitation.

Amendments to the Protocol

All essential amendments to this protocol will be discussed and decided among the core study team (JG, STK, RC) and communicated among the wider team of reviewers. Amendments will be documented, specifying the timing and rationale for each amendment, added to the PROSPERO study entry, and reported in the final study report.

Results

Data collection started in September 2020 and the literature search was updated in July 2021. Data synthesis is ongoing and the literature search will be updated in October 2022.

Discussion

Contribution to the Literature

To reach the objectives specified above, several methodological considerations and decisions have informed the protocol for this systematic review. One early principal decision in the review's conceptualization was to search for data on determinants of physical activity behavior instead of searching for experimental evidence of behavior change interventions for physical activity in people with CVD. Both approaches are possible, depending on the objectives of interest. For example, systematic reviews and meta-analyses by Silva et al [31] and Bélanger-Gravel et al [32] collated experimental evidence of implementation intention interventions (eg, action planning) on physical activity behavior in mixed populations, including studies with healthy and general population samples as well as different clinical groups. These reviews were able to show small to moderate pooled effect sizes of intention interventions on physical activity, as eligibility criteria were a priori theoretically driven and included interventions based on the Theory of Self-Regulation and Theory of Planned Behaviour, resulting in the inclusion of theoretically coherent primary study interventions [31,32]. In this example of previous studies, the focus is on *interventions* targeting physical activity.

For physical activity behavior in the cardiac rehabilitation population, this approach may present limitations due to various and complex intervention concepts that have been trialed in the past, with differing and sometimes unspecified or poorly described underlying theoretical mechanisms of action. It is a recognized limitation in the literature on complex health care *interventions* that authors provide limited details on the underpinning theoretical approach, assumptions of mechanisms of action, and actual content and implementation of interventions [33,34]. For this reason, a decision was made to search for observational evidence of *determinants* of physical activity behavior in this target population, which relates more directly to understanding influences on behavior and is therefore likely to prove more informative for developing novel contextualized intervention concepts than experimental evidence of intervention effectiveness.

The systematic review and meta-analysis by Amireault et al [35] has a comparable focus area to this review and investigates the *determinants* of physical activity maintenance with potential long-term effectiveness to inform future interventions. However, its target population is healthy adults. Determinants of physical activity may be different for the cardiac rehabilitation population compared to healthy adults, as health conditions, comorbidities, and physiological factors such as kinesiophobia [36] may determine physical activity behavior differently in the cardiac rehabilitation population.

Another review with similar focus was published by Petter et al [37]. The authors collated evidence of social-ecological correlates of exercise in people with coronary heart disease and described 32 factors based on 121 included studies. The review by Petter et al [37] differs from this review in two key aspects. First, due to the lack of detailed reporting of association statistics, Petter et al [37] were unable to synthesize precise association statistics (as is the aim in this review) but interpreted the presence of associations across studies, that is, based on the number of studies supporting certain hypothesized associations (*detailed group procedure*). While this is a valid and useful approach, it is anticipated that our review will add value through synthesizing quantified associations from reported association statistics, thus enabling a more informed judgement on the relative importance of different determinants. Second, most studies included in the review by Petter et al [37] provided data on people's exercise adherence during formal center-based and home-based cardiac rehabilitation, as opposed to sustained maintenance of heart-healthy physical activity outside of formal cardiac rehabilitation provision, which is the aim of this review.

In the definition of the study population, this review will focus on people with a medical indication for cardiac rehabilitation because this implies a recommendation for lifelong regular heart-healthy physical activity. It also indicates that this target population would (or should) enter formal clinical rehabilitation settings or have other encounters with cardiac clinical services (follow-up appointments, written communications), providing touchpoints at which theoretically and empirically informed behavior change interventions for sustainable healthy habit formation could ideally be leveraged. In the finalized search strategy, the search terms for relevant medical diagnoses were therefore combined with descriptors for cardiac rehabilitation, suitably contextualizing the search to the cardiac rehabilitation clinical pathway.

It was a deliberate decision, in the selection of the outcome for the systematic review, to focus on physical activity behavior as opposed to exercise capacity. Exercise capacity describes an individual's physical fitness and constitutes a critical cardiac rehabilitation outcome. Typically, it is assessed through standardized ergometry [38] or other individual fitness tests such as the 6-minute walking test [39]. However, in this review, the focus lies on a more directly relatable outcome: habitual physical activity behavior in the target population, which also

links to the official international recommendation for physical activity provided by the World Health Organization [40]. Moreover, the focus of interest in this review lies on individuals' habitual physical activity behavior in the context of their everyday lives. Therefore, studies of attendance at or completion of cardiac rehabilitation exercise sessions will be excluded, as will studies of adherence to professionally guided home- or community-based exercise training interventions for people with CVD because these are generally highly resourced, time-limited, and not reflective of ongoing self-initiated heart-healthy physical activity behavior.

In defining the outcome of physical activity behavior, a deliberate decision was made to include both self-reported and tracked outcome data. It is often asserted that tracked (*objective*) physical activity measurements, for example, using accelerometers, pedometers, smartphones, or wearables, are preferable to self-reported (*subjective*) physical activity measures due to biases inherent in self-report methods, including misperception, recall bias, or social desirability bias [34,41]. For example, in a study of 1751 adults across ages 19 to 84, a comparison of self-reported (International Physical Activity Questionnaire) and tracked (ActiGraph accelerometer) physical activity over a 1-week period indicated that, on average, sedentary time was underreported and vigorous physical activity was overreported [42]. However, it may be helpful to view self-reported and tracked physical activity measures as two alternative or even complementary approaches, each with their advantages and disadvantages. Tracked physical activity measurements can be susceptible to technical failure or operator error, for example, when wearable devices are given out to study participants for more extended time periods and rely on participants for accurate application, handling, and recharging of the device. Other limitations of physical activity measurement devices include the inability to capture all types of activity automatically (in particular, swimming, cycling, and individualized exercise; eg, strength training can be difficult to detect), heterogeneity in device capabilities and data analytic processes, the burden of wear time for participants, and potential for high reactivity (ie, the impact of wearing a tracking device on the participant's physical activity behavior) [43]. Advantages of self-reported physical activity measures are lower participant burden, cost, and time requirements of administration, particularly for one-off retrospective self-reporting of physical activity behavior (International Physical Activity Questionnaire [44]) as opposed to the daily completion of a physical activity diary or description of physical activity during *typical* time periods (Godin-Shephard Leisure-Time Physical Activity Questionnaire [45]).

Limitations

Limitations of this systematic review are acknowledged. First, a date filter (2005 and later) is applied to the literature search. While this date filter is intended to identify studies more reflective of recent cardiac patient profiles under state-of-the-art medical and rehabilitation care, determinants of physical activity reported prior to 2005 may nevertheless be of relevance. Future research could extend the search parameters to include studies published prior to 2005 as well. Second, the results are restricted to peer-reviewed literature. This could lead to potential publication bias due to missing null results that are more likely to be disseminated in conference abstracts and gray literature than in peer-reviewed articles. Future research could address this limitation by widening eligibility criteria in addition to seeking access to unpublished data sets if necessary.

Conclusions

Considering those beforementioned methodological aspects, this review will be valuable to relevant stakeholders, including clinicians and health care professionals, intervention developers, and decision makers in health care. It will shed new light on the relevance and significance of modifiable (eg, health belief, health literacy, illness cognition, or structural barriers for executing physical activity behavior) and nonmodifiable (eg, sociodemographics, education, health insurance, or income) determinants of physical activity to maintain physical activity behavior.

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Authors' Contributions

JG, STK, JN, and RC conceptualized this study. JG, STK, and RC curated the data and designed the methodology. JG was the project lead. STK and RC supervised the study. JG validated and provided visualizations for the study, as well as wrote the original draft. JG, STK, JN, and RC reviewed and edited the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.

[DOCX File , 30 KB - resprot_v11i9e39188_app1.docx]

Multimedia Appendix 2
Search strategies for a systematic review on determinants of physical activity in the cardiac population.
[DOCX File , 31 KB - resprot_v11i9e39188_app2.docx]

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Abbreviations

CVD: cardiovascular disease
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Technologies for Interoperable Internet of Medical Things Platforms to Manage Medical Emergencies in Home and Prehospital Care: Protocol for a Scoping Review

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Abstract

Background: Population growth and aging have highlighted the need for more effective home and prehospital care. Interconnected medical devices and applications, which comprise an infrastructure referred to as the Internet of Medical Things (IoMT), have enabled remote patient monitoring and can be important tools to cope with these demographic changes. However, developing IoMT platforms requires profound knowledge of clinical needs and challenges related to interoperability and how these can be managed with suitable technologies.

Objective: The purpose of this scoping review is to summarize the best practices and technologies to overcome interoperability concerns in IoMT platform development for medical emergencies in home and prehospital care.

Methods: This scoping review will be conducted in accordance with Arksey and O'Malley's 5-stage framework and adhere to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols) guidelines. Only peer-reviewed articles published in English will be considered. The databases/web search engines that will be used are IEEE Xplore, PubMed, Scopus, Google Scholar, National Center for Biotechnology Information, SAGE Journals, and ScienceDirect. The search process for relevant literature will be divided into 4 different steps. This will ensure that a suitable approach is followed in terms of search terms, limitations, and eligibility criteria. Relevant articles that meet the inclusion criteria will be screened in 2 stages: abstract and title screening and full-text screening. To reduce selection bias, the screening process will be performed by 2 reviewers.

Results: The results of the preliminary search indicate that there is sufficient literature to form a good foundation for the scoping review. The search was performed in April 2022, and a total of 4579 articles were found. The main clinical focus is the prevention and management of falls, but other medical emergencies, such as heart disease and stroke, are also considered. Preliminary results show that little attention has been given to real-time IoMT platforms that can be deployed in real-world care settings. The final results are expected to be presented in a scoping review in 2023 and will be disseminated through scientific conference presentations, oral presentations, and publication in a peer-reviewed journal.

Conclusions: This scoping review will provide insights and recommendations regarding how interoperable real-time IoMT platforms can be developed to handle medical emergencies in home and prehospital care. The findings of this research could be used by researchers, clinicians, and implementation teams to facilitate future development and interdisciplinary discussions.

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KEYWORDS

interoperability; Internet of Medical Things; prehospital; home care; reference models; mapping; technologies; scoping review, falls, cardiovascular disease, stroke; medical emergency; home care; prehospital care

Introduction

Background

Advancements in wireless technology, artificial intelligence, and sensor technology have enabled the use of remote patient monitoring as a method to prevent and detect medical emergencies [1]. This includes, for example, cardiovascular diseases [2], stroke [3], sepsis [4], and trauma, including falls, which together claim millions of lives each year [5-7]. These medical emergencies can often be attributed to population aging, as elderly individuals are more susceptible to disease and disability. Between 1990 and 2017, the 2 main causes of disease-specific deaths globally attributed to population aging were ischemic heart disease (3.2 million) and stroke (2.2 million) [8]. Other diseases that notably contribute to deaths among older adults (≥65 years) are heart failure (20%), dementia (13.6%), chronic lower respiratory disease (12.4%), and pneumonia (5.3%) [9]. Furthermore, degenerative diseases and arthritis gradually decrease individuals' physical and mental capacities and have all been associated with a high incidence of life-threatening falls among elderly individuals [10,11]. As of 2021, falls are the second leading cause of all unintentional injury deaths worldwide [12].

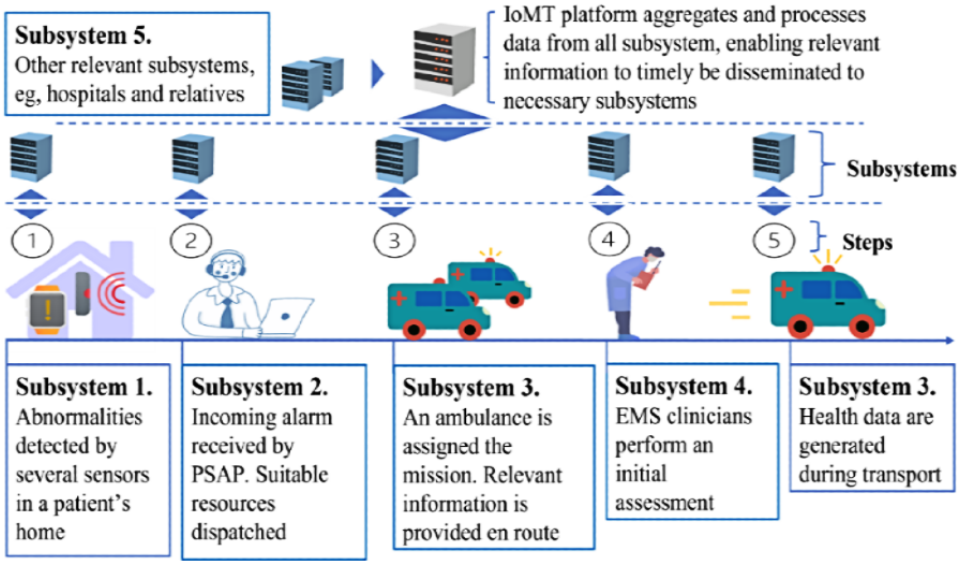
Globally, medical emergencies impose a great economic burden. In 2015, the estimated medical costs attributable to fatal and nonfatal falls among elderly individuals (≥65 years) in the United States were approximately US $50 billion [13]. The estimated global cost of stroke is over US $891 billion, which is 1.12% of the global gross domestic product (GDP) [14]. Population growth and population aging further indicate that additional economic strain will be put on future health and social systems [15]. In 2020, Li et al [16] showed that the health care expenditure per capita in China of the age group ≥65 years was 7.25 times higher than the health care expenditure per capita of the age group ≤25 years. In the United States, people aged 55 and over account for more than half of total health spending [17]. In Sweden, the municipalities' total cost of elderly care in 2020 was 135 billion SEK (approximately US $14 billion), an increase of more than 40% from the costs of 96 billion SEK (approximately US $10 billion, inflation considered) in 2010 [18].

Supporting the health and well-being of a growing population in the context of an aging population remains one of today's most complex and critical global challenges [19]. More health care must be provided closer to patients' homes to reduce health care costs and optimize health care processes [20]. This transition of health care motivates the need for technical solutions that can support its success. Several interconnected medical devices and applications, an infrastructure referred to as the Internet of Medical Things (IoMT), are suitable approaches for remote patient monitoring [21]. IoMT can increase patient safety, reduce health care costs, and streamline processes and workflows in home and prehospital care [1]. In the IoMT, devices communicate over the internet to achieve a common goal [22,23]. Furthermore, combining several devices, followed by adequate data fusion, can be advantageous in terms of system accuracy [24].

Home care is the provision of health care in patients' homes with the goal of complementing and replacing hospital care and improving quality of life [25] (Step 1 in Figure 1). Prehospital care refers to emergency medical services (EMS) provided to a trauma victim before they arrive at the hospital (Steps 2-5 in Figure 1). Together, home care and prehospital care include several steps: remote monitoring, health status assessment, resuscitation, and stabilizing measures [26]. Each step is associated with data generation and data processing. The sensors in Step 1 in Figure 1 can be deployed in a patient's home, and in the case of detected abnormalities, an alarm can be sent to the public safety answering point (PSAP). For an adequate care process and patient safety, the information must rapidly and securely flow through each step in Figure 1.

Today's systems often lack the functionality necessary to manage all the steps depicted in Figure 1 [27]. Some studies have focused on different algorithms (eg, predicting the need for critical care [28], fall detection and fall prevention [29-31], certain sensor setups, pressure sensors [31], and radio frequency [32,33]) or certain levels of interoperability (semantic interoperability [34-37]). For systems to function effectively in both home and prehospital care, the whole scenario must be considered, and several interoperability challenges must be addressed. These challenges include (1) interoperability of the real-time data collection system, involving integration of devices and platforms from different vendors, allowing data fusion as a technique to increase system accuracy (Step 1, Figure 1) [24]; (2) interoperability in the data stored in disparate systems, such as medical devices, electronic health records (EHRs), emergency service centers, and emergency medical dispatch systems (subsystems, Figure 1); (3) definition of mechanisms for the dissemination of data to third-party applications; and (4) services for big data processing and knowledge extraction. According to Rubí and Gondim [27], prior studies have partially solved these challenges, although without considering the whole scenario. For information to flow through each step in Figure 1, all challenges 1-4 must be solved. In this scoping review, the focus is on interoperable IoMT platforms that address the interoperability challenges 1-4 and cover Steps 1-3 in Figure 1.

Figure 1. Example of events and data being transferred through several subsystems in home care and prehospital care settings. EMS: emergency medical services; IoMT: Internet of Medical Things; PSAP: public safety answering point.

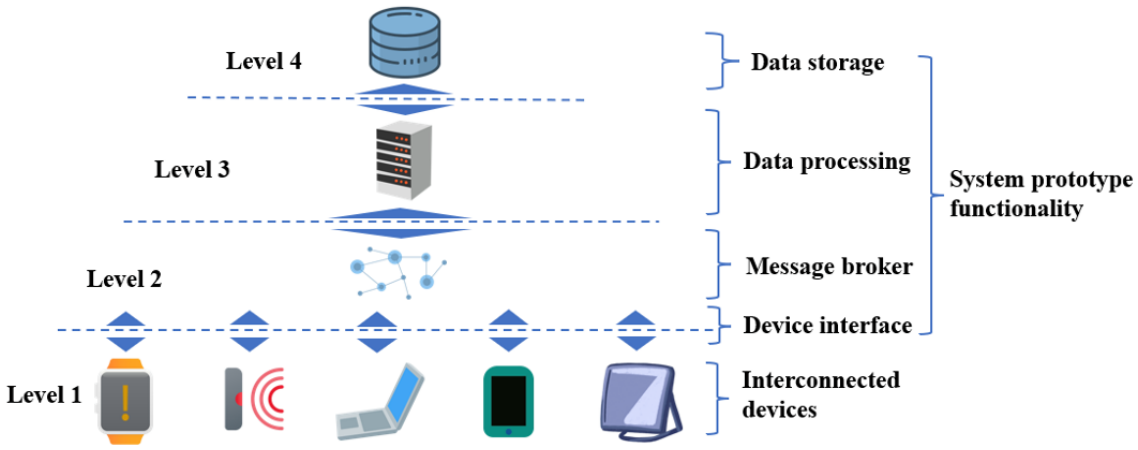


The ASAP (Acute Support, Assessment, and Prioritizing) Project

The World Health Organization (WHO) has declared falls as a major public health problem [12]. Over 37 million severe falls are reported globally each year among older adults (≥65 years). Approximately 684,000 individuals die from falls each year, a number that is projected to increase due to population aging [12]. Hip fractures, traumatic brain injuries, and upper limb injuries are all examples of injuries following severe falls, and if appropriate treatment is not received in time, the injury can worsen [38]. Various postfall syndromes, such as confusion, immobilization, and depression, may place further constraints on daily activities several months after the fall [12]. According to the Swedish National Board of Health and Welfare, the costs for falls in Sweden amount to 17 billion SEK (approximately US $1.7 billion) [39].

As a response to population aging and the need for more efficient home and prehospital care, an ongoing research project led by Chalmers University of Technology in Gothenburg, Sweden, aims to tackle these concerns in a project named ASAP (Acute Support, Assessment, and Prioritizing). Since falls account for 40% of all injury-related deaths among persons aged 85 years or older [10], the ASAP project's initial focus is on falls. The aim of the ASAP project is to develop an interoperable system prototype (Figure 2) for home care and prehospital care, meaning that the system prototype will encompass functionalities necessary to manage Steps 1-3 in Figure 1, from the moment a person falls in their home until the paramedics arrive at the scene. Even though falls are the platforms' initial focus, functionalities to manage additional medical emergencies such as congestive heart failure, arrhythmia, and stroke will be targeted in future system development processes.

Figure 2. Simplified architecture visualizing the building blocks of the Internet of Medical Things (IoMT). In the ASAP (Acute Support, Assessment, and Prioritizing) project, the aim is to develop an interoperable system prototype that includes functions covered by Levels 2–4.

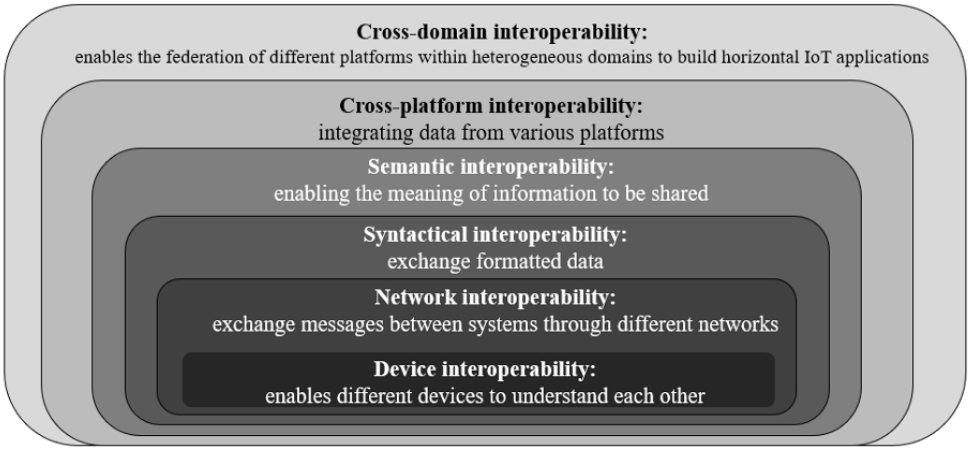


Interoperability Model

Today, a great deal of health-related information is hidden in isolated data silos and incompatible systems, making it difficult to access and use this information [27]. However, medical emergencies require that information be exchanged rapidly and securely between systems [38]. For this interplay to function adequately, different devices and applications must be

interoperable; they must access, exchange, and use information in a predictable and standardized manner [40-42]. Interoperability has recently received increased attention due to the need to uncover the full potential of big data and improve digital health. However, the precise meaning of the term interoperability is ambiguously defined [41,42]. Several definitions exist, and numerous attempts have been made to present the concept using different models [42]. In this scoping review, the term interoperability is conceptualized through a 6-level hierarchical structure (Figure 3) [42].

Figure 3. Interoperability model visualizing the different levels of interoperability. Each level is associated with different interoperability challenges.

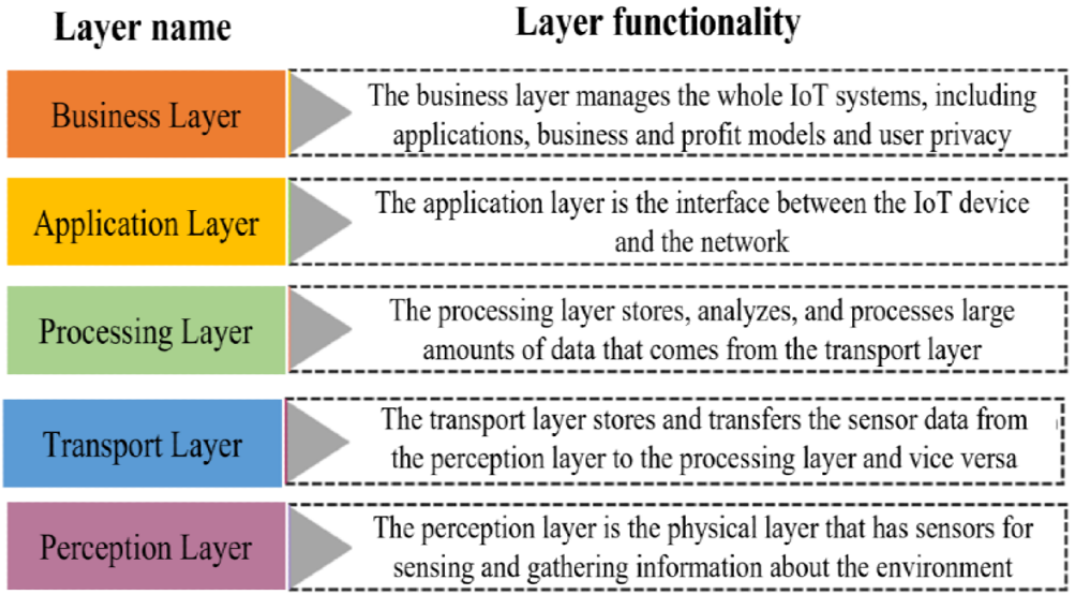


Internet of Things (IoT) Architecture and Reference Models

Software-defined networking (SDN) [42-44] and computational infrastructures (such as fog computing [45,46]) have been identified as potential technologies needed to cope with latency and bandwidth problems due to congested networks [43,45]. These and other technologies have the potential to solve many of today's interoperability challenges. Different protocols, a set of rules that allow machines and applications to exchange information [47], also play a key role in solving interoperability challenges. Together, different protocols form reference models (also called protocol stacks, Figure 4), which provide a structured way to discuss system components and system functions [23,47]. Knowledge of these models and technologies can facilitate the development of IoMT architectures [23] (Figure 2).

In this scoping review, technologies refer to approaches used to implement the IoMT building blocks in Figure 2. The IoMT reference model in Figure 4 further helps to conceptualize these building blocks. Technologies are limited to data formats and protocols (Level 1), middleware technology and application programming interfaces (APIs; Levels 2-4), computational infrastructures, data processing techniques (Level 3), data storage (Level 4) and standards, and network architectures (Levels 1-4). Hardware, project management processes, and regulatory compliance are not considered. The aim is to provide recommendations regarding suitable technologies that can be used to develop interoperable IoMT platforms and help to achieve the levels of interoperability presented in Figure 3.

Figure 4. Different levels of an Internet of Medical Things (IoMT) reference model. Each layer is associated with different protocols and technologies, all of which help realize each layer's specific functionality. The model helps to conceptualize IoMT building blocks.



Previous IoMT Platform Development

Efforts from digital health global research communities have addressed concerns related to remote patient monitoring. Takatou and Shinomiya [48] developed an IoMT-based real-time fall detection prototype system for elderly individuals in 2020 using passive radio frequency identification (RFID) sensor tags. Rachakonda et al [49] presented Good-Eye in 2020, an IoMT-enabled device that can both detect and predict fall-related accidents using data fusion techniques. Good-Eye was able to predict falls with an accuracy of 95%. For validation of the Good-Eye system, 6 study participants and 144 different instances of sitting and falling were recorded with the use of depth cameras. Kommey et al [50] proposed a patient medical emergency alert system (PMEAS) that allows body temperature and heart rate to be collected and transmitted to the user's phone via Bluetooth. The PMEAS accurately recorded the temperature of the user approximately 80% of the time [50]. Vandenberk et al [51] developed DHARMA, a component-based digital research platform for mobile remote monitoring studies. The DHARMA platform performed well in a real-time health care setting for the follow-up of pregnant women at risk of developing preeclampsia.

Although many solutions have promising results regarding the detection of abnormal values [49-53], research tends to focus on certain aspects of the problem concerning remote patient monitoring. For an IoMT platform to be integrated and employed in real-life settings, these platforms must be capable of managing multiple devices and their different characteristics (ie, different communication protocols and data formats) [54]. The lack of standards for data integration and deficient integration capabilities with external platforms and EHR systems impedes the usage of IoMT platforms in real life [40,54]. To date, little attention has been given to real-time systems that can be deployed in real-world care settings [27]. Therefore, more comprehensive studies that focus on effective and secure data transmission and management are needed.

Related Work

Related studies have previously been conducted. Ait Abdelouahid et al [55] focused on a map between IoT communication protocols and an 8-level interoperability model. Garai and Adamkó [56] mapped a 3-level interoperability model against the 7-layer Open Systems Interconnection (OSI) model. Tayur and Suchithra [57] examined current standards, data formats, and protocols to overcome interoperability issues, focusing on the application layer. Leite et al [58] and Noura et al [42] examined technologies used to overcome interoperability concerns in the IoT. Sethi and Sarangi [23] presented a survey of the current technologies used in the IoT domain as of 2016. To our knowledge, there has been no previous study that combines interoperability challenges and suitable technologies with a focus on medical emergencies. This type of study is necessary to obtain an overview of how interoperable real-time IoMT platforms can be developed, which types of interoperability issues can arise, and how these can be managed with suitable technologies.

Aim

This scoping review aims to summarize suitable technologies and best practices used during the development process of real-time interoperable IoMT platforms, with a focus on platforms that can handle medical emergencies, such as falls, congestive heart failure, and stroke, in home and prehospital care settings. The overall goal is to summarize and describe technologies used to overcome interoperability concerns. Furthermore, the aim is to provide recommendations regarding the technologies used to develop interoperable IoMT platforms, enabling clinicians and practitioners to understand relevant challenges and use appropriate techniques to tackle these concerns. Technical concepts will be described based on how they can be used in health care, enabling clinicians and nontechnical professionals to understand their application areas.

Methods

Overview

Arksey and O'Malley [59] describe 4 common reasons why it can be worthwhile to undertake a scoping review. The third reason is "to summarize and disseminate research findings" [59]. This description can best be applied to this scoping review. Hence, the aim is to summarize and disseminate research findings within the frontiers between clinical applications, interoperability, and IoMT platform development. Our scoping review protocol will be based on Arksey and O'Malley's 5-stage methodological framework for scoping reviews [59]. In this model, Stage 1 consists of identifying the research question. Stage 2 involves identifying the relevant studies. Stage 3 comprises study selection. Stage 4 consists of charting relevant data from the studies. Stage 5 consists of collecting, summarizing, and reporting the results

If necessary, these stages will be further broken down into more manageable substeps to increase the transparency of the method. The electronic databases/web search engines used in the study are IEEE Xplore, PubMed, Scopus, Google Scholar, NCBI, SAGE Journals, and ScienceDirect, as these search engines have been previously used by related studies.

The scoping review protocol is reported in accordance with the reporting guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) statement. The PRISMA-P checklist was developed for a systematic review protocol; therefore, not all items will be covered (see Multimedia Appendix 1).

Stage 1: Identification of the Research Question

A preliminary search of the literature was conducted. The aim was to outline important keywords to refine the search terms used in the review and to develop relevant research questions. Studies were screened by title and abstract to determine suitability for inclusion. Several abbreviations, terms, and acronyms that were found in the literature and deemed to be relevant were noted and tabulated (Textbox 1). To decide whether a term, abbreviation, or acronym should be tabulated, it had to fulfill 2 criteria. First, it had to be considered a keyword that could help the reviewers search for literature that could be used to identify relevant research questions. Second, it had to

be a new keyword. These new keywords were, however, combined with other familiar search terms using the Boolean operators AND and OR (Figure 5). Stage 1 was completed with this scoping protocol.

In addition, a snowball approach described by Wohlin [60] was used to further screen for new articles. Snowballing refers to using the reference list of a paper (backward snowballing) or the citations to the paper (forward snowballing) to identify additional papers [60]. Both backward and forward snowballing were used in Stage 1. The identified articles were continuously saved to the reference manager Mendeley (version 2.70; Elsevier), and duplicates were removed.

Textbox 1. Examples of abbreviations, terms, and acronyms relevant for Internet of Medical Things (IoMT) platform development.

Standards

- FHIR (fast health care interoperability resources)
- oneM2M
- openEHR
- SenML (Sensor Markup Language)

Network/software architectures

- Multitenancy
- SDN (software-defined networking)
- SOA (service-oriented architecture)

Internet of Medical Things (IoMT) platform/software frameworks

- Aneka
- FogBus
- GiraffePlus
- GoodEye
- HealthGo
- HPCaaS (high-performance computing as a service)

Protocols

- AMQP (Advanced Message Queueing Protocol)
- CoAP (Constrained Application Protocol)
- IPv6 (Internet Protocol version 6)
- MAC (media access control)
- MQTT (Message Queuing Telemetry Transport)
- RDP (Remote Desktop Protocol)
- SCAIP (Social Care Alarm Internet Protocol)
- Websockets
- XMPP (Extensible Messaging and Presence Protocol)

Computational infrastructures/systems

- Apache Flink Apache Kafka
- Apache Storm
- Fog computing
- Multiaccess edge computing
- Edge computing

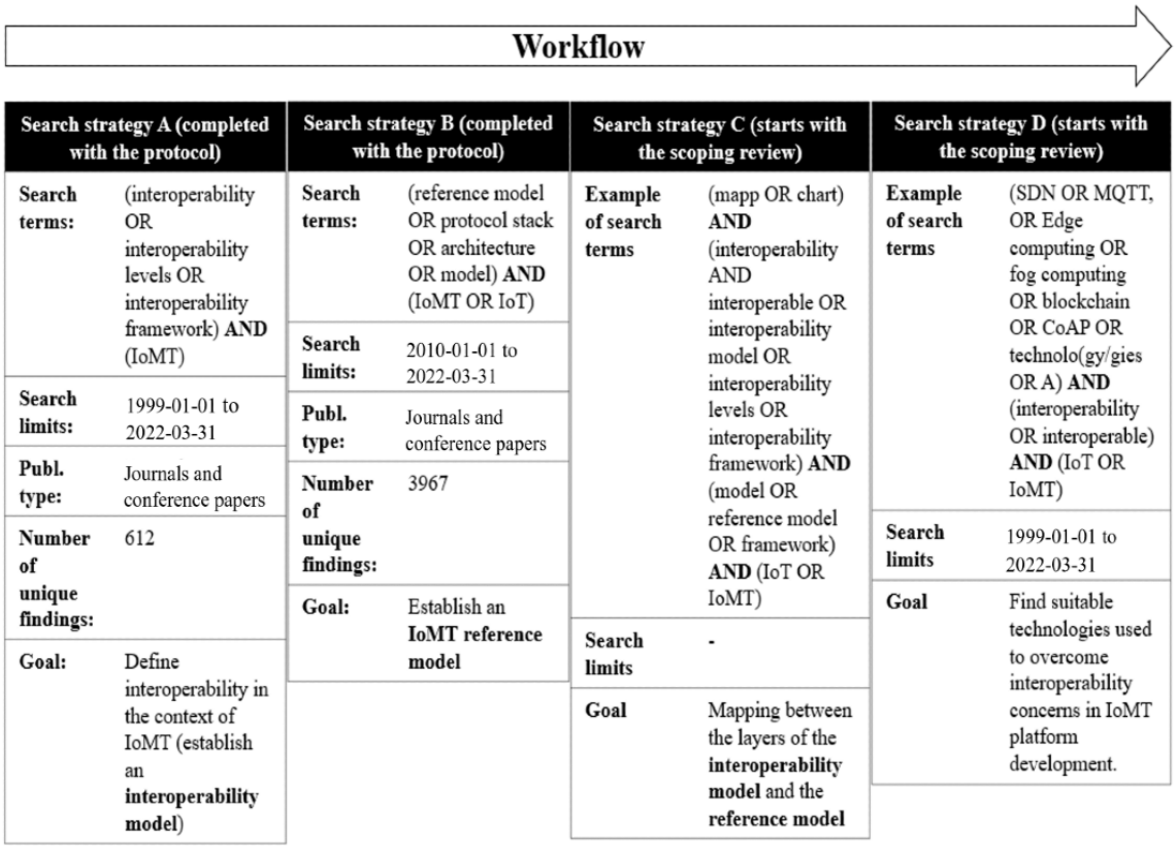
Data management

- Blockchain
- Stream reasoning

The following research questions were identified:

1. What are the current challenges of developing a real-time IoMT platform for managing medical emergencies such as falls?
2. What is interoperability, and how can it be defined in the context of the IoMT?
3. What types of models are used to visualize the different layers of interoperability? When talking about medical devices in an IoMT setting, which model is preferable and why?
4. Which reference model with corresponding protocols can best describe and define the structure of key aspects of the information being managed in a real-time IoMT system? How is the model being used today?
5. Have any studies examined which current technologies are associated with the layers in the reference models identified in research question 3, and how these are being used to fulfill the set of rules defined by each layer? If so, what are the results?
6. How can interoperability solutions be mapped to the layers in the interoperability model?
7. What recommendations regarding technologies can be given to clinicians and practitioners who want to develop interoperable IoMT platforms for home and prehospital care settings?

Figure 5. The different search strategies. IoMT: Internet of Medical Things; IoT: Internet of Things; MQTT: Message Queuing Telemetry Transport; SDN: software-defined networking.



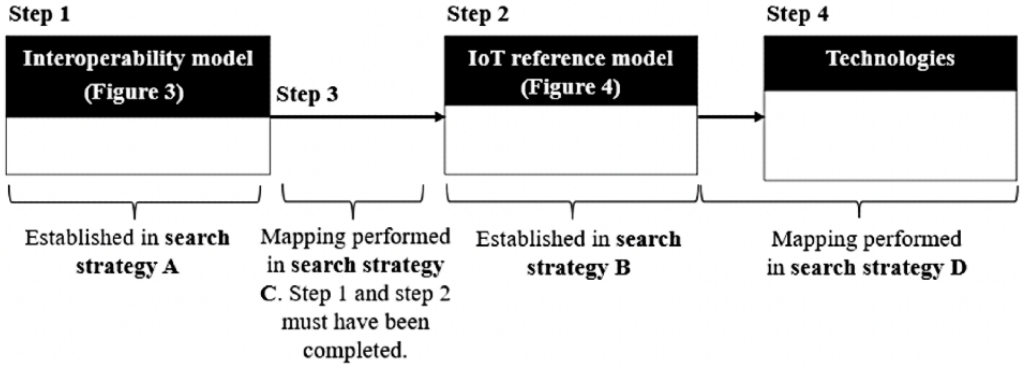
Stage 2: Identification of Relevant Studies

To answer the research questions outlined in Stage 1, a comprehensive search strategy will be conducted. Since the scoping review encompasses a broad spectrum of research questions, the search process will be divided into 4 search strategies with separate search terms, search limits, and goals (Figure 5). Strategies A-D will be carried out in chronological order, starting with search strategy A. Search strategies A and B were completed with this protocol.

The chronological workflow structures the work into more manageable pieces and ensures that any prior knowledge deemed necessary for each search strategy has been acquired in the previous step. Figure 6 shows the reasoning behind the chronological workflow and provides an overview of how the search strategies relate to each other.

Backward and forward snowballing was used in Steps A and B and will further be used in Steps C and D. The final inclusion of a paper will be based on the eligibility criteria in Textbox 2. These criteria will be applied in all steps.

Figure 6. Reasoning behind the chronological workflow. The workflow is carried out in the following order: Step 1, Step 2, Step 3, and Step 4. IoT: Internet of Things.



Textbox 2. Inclusion and exclusion criteria. IoMT: Internet of Medical Things; IoT: Internet of Things.

Inclusion criteria

- Published peer-reviewed journals and conference papers
- Written in the English language
- Published during the time period defined in the protocol
- Studies describing or reporting the development or design of IoMT systems with a focus on the technology
- Studies reporting challenges and barriers of integrating IoMT platforms into prehospital care or home care settings with a focus on the technology
- Studies describing different relevant technologies used for IoMT platform development

Exclusion criteria

- Full-text articles that could not be obtained and/or are not written in English
- Conference abstracts, book reviews, commentaries, and editorial articles
- Studies focusing on hardware, project management processes, or regulatory compliance
- Studies reporting on the design or development of IoT applications with no focus on health data (eg, Industry 4.0, including the automotive industry, food industry, manufacturing industry, etc).

Search Strategy A: Defining Interoperability

Search strategy A covered the concept of interoperability. It was completed with this protocol and resulted in the interoperability model (Figure 3). It laid the foundation regarding what interoperability concerns and helped establish an interoperability model that we can proceed from (Figure 3). Since the term interoperability is hard to define and numerous conceptual frameworks exist, the aim was to find a model best suited for the purpose of this scoping review (ie, reviewing software technologies associated with interoperability concerns in IoMT settings). Hence, the aim of strategy A was to cover articles published between January 1, 1999, and March 31, 2022, since the term “Internet of Things” appears to have been first coined in 1999 by Kevin Ashton [61], whereas the term “interoperability” appears to have been around since 1970 [62].

Search Strategy B: IoT Reference Models

Search strategy B covered reference models. It was completed with this protocol and resulted in the reference model (Figure 4). The focus was on models used to describe the interface between different components in an IoT setting, since knowledge of the architectural structure of reference models is necessary in software development [23]. Due to the rapid increase in the number of interconnected devices in recent years [63] and to limit the search results, search strategy B was limited to studies published between January 1, 1999, and March 31, 2022.

Search Strategy C: Mapping Between the Interoperability Model and the IoT Reference Model

In search strategy C, we will proceed from Figures 3 and 4. Strategy C will start with the scoping review. The goal is to map the levels in the interoperability model (Figure 3) to the corresponding levels in the reference model (Figure 4). Similar mappings as suggested in the literature will be examined and used as a reference [61]. Each mapping will be performed according to the layer(s) in the reference model in which different interoperability challenges appear (Figure 7). This will be followed by an explanation of the motivation regarding the terms on which the mapping has been performed. Two separate models can name their layers differently but describe the same concept or model functionality. Therefore, the mapping process will be systematically conducted following the process described in Figure 8.

Figure 7. Example of mapping between the layers in an interoperability model and the layers in a Transmission Control Protocol/Internet Protocol (TCP/IP) model. In this case, challenges related to semantic interoperability can arise at the application layer of the TCP/IP model.

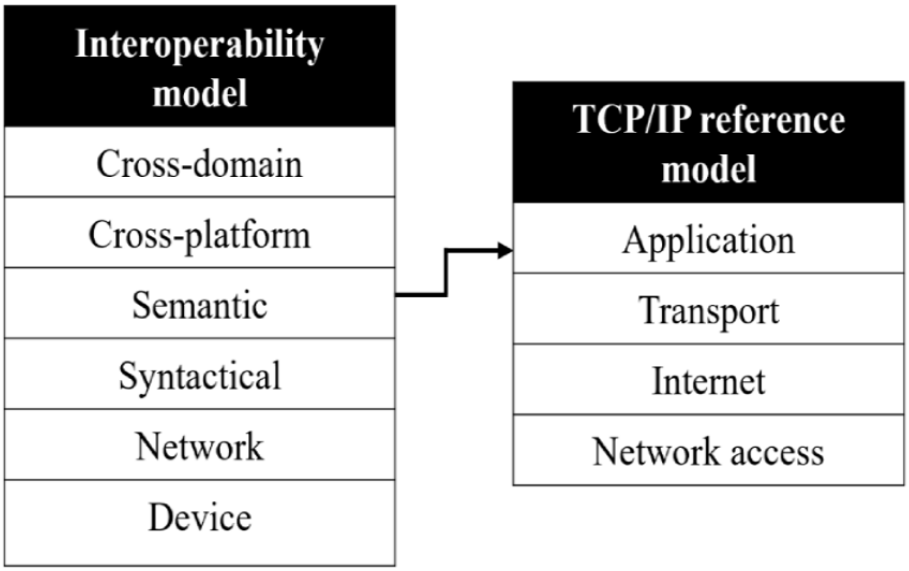
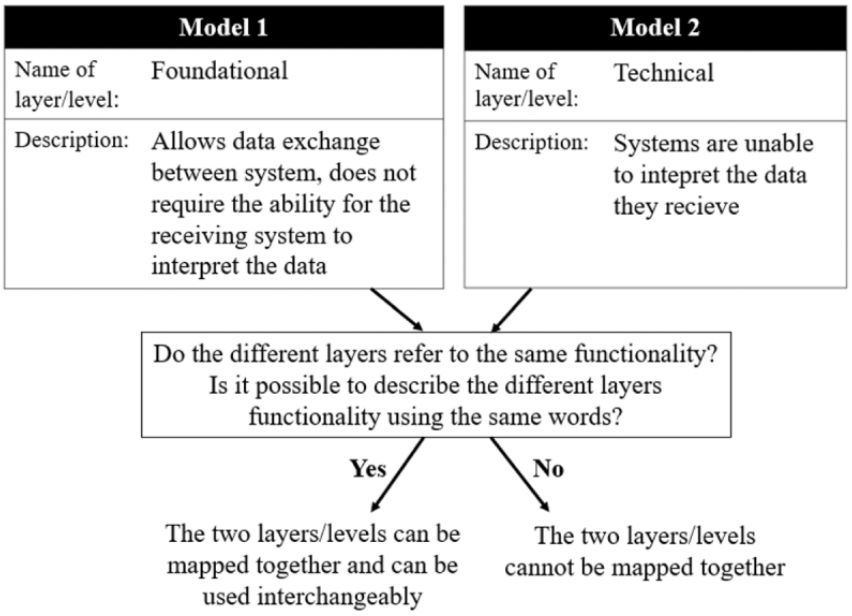


Figure 8. Schematic overview of the mapping process. In this case, the 2 layers can be mapped together.



Search Strategy D: Technologies

Strategy D will cover technologies used to overcome interoperability challenges during the development process of real-time interoperable IoMT platforms. In this step, we will proceed from Figure 3. Technologies will be tabulated and followed by a descriptive overview regarding how that technology can be applied in the context of IoMT platform development to handle medical emergencies (Figure 7). Search terms specified in Figure 5 will be complemented with terms from Textbox 1. Articles describing the development process of IoT platforms [64] will be of particular interest since these often cover several aspects regarding the development process and thus act as a source of information from which new technologies and search terms can be obtained.

The majority of standard IoT protocols were developed in the late 1990s or during the 21st century. For example, the Constrained Application Protocol (CoAP) was published as a full Internet Engineering Task Force (IETF) internet standard in 2014, the Advanced Message Queuing Protocol (AMQP) was created in 2003, and Message Queuing Telemetry Transport (MQTT) was created in 1999 [65]. Therefore, the search strategy will be limited to articles published between January 1. 1999, and December 31, 2022. This limitation is further motivated by the fact that new emerging concepts such as SDN (2008) [43], fog computing (2012) [66], and blockchains (2008) [67] have been introduced over the past 2 decades.

Stage 3: Study Selection

Studies will be selected based on 2 screening processes. To facilitate the screening processes, several inclusion and exclusion criteria were developed (Textbox 2). Inclusion criteria will be adapted in both screening processes.

Title and Abstract Screening

The first screening process will include an evaluation and an assessment of the relevance of the articles' titles and abstracts. Rayyan (Rayyan Systems Inc) will be used by 2 reviewers in the group (authors MS, HJ) to reduce any biases. Rayyan is a free mobile and web tool designed to help researchers work on knowledge synthesis projects, including scoping reviews [68]. The 2 reviewers will perform the screening process independently of each other. In case of any disagreements, a third member of the research team will vote regarding whether the article should be included. Inclusion or exclusion will then be based on the majority decision. All 3 reviewers will use the same inclusion and exclusion criteria when deciding whether an article should be included. Decisions will be based on majority vote.

Full-Text Screening

The articles that pass the title and abstract screening will undergo a second screening stage. This stage involves a full-text review conducted in the same way as the first screening process.

Stage 4: Charting the Data

In this stage, only articles that pass title and abstract screening and full-text screening will be summarized. Information relevant for extraction will include general findings that are shared among the articles that are to be summarized. These findings include author(s), year of publication, country of origin, purpose/aim of the study, methodology, type of study, and outcomes. In addition to these general findings, more specific information that will help answer each research question will be summarized, including the following: (1) What technologies are used to develop real-time interoperable IoT/IoMT platforms? (2) How are the technologies used? (3) For what purposes are the technologies used? This will include information about the models used, technological approaches and their pros and cons, research context, challenges and barriers, conclusions, and future work.

To map the findings regarding technologies to corresponding layers in the reference model, the extracted data will be categorized using the web application Dedoose (SocioCultural Research Consultants), a qualitative data analysis application [69]. The focus will be on qualitative data. Quantitative evaluations or measurements of system performance will not be considered. The coding scheme will be tested by 2 separate members (authors MS, HJ) of the team to ensure that it is a suitable and applicable scheme.

Stage 5: Collating, Summarizing, and Reporting the Results

In this stage, findings from the reviewed literature will be summarized and presented. The summary will include both a descriptive summary and a thematic analysis. Qualitative analysis techniques will be used to complete the thematic analysis. Models established in Stages 1 and 2 will be visualized through images and described in running text. The mapping conducted in search strategy C will be visualized through models and tables. Findings (technologies) from search strategy D will be tabulated together with a definition and a description in running text. Findings from search strategy D will also form the basis for recommendations on suitable technologies that can be used during the development of interoperable IoMT platforms.

The result will provide an overview of how and why different interoperability concerns appear at different stages during the software development process and how these can be managed through the usage of suitable technologies. If the same technology is examined and recommended in multiple studies, the number of occurrences will be summarized and reported. Although the focus is on real-time IoMT platforms, the result will hopefully be valuable to a broad audience working with IoMT applications. Because an assessment of study quality is not routinely used in scoping reviews [69,70], this kind of assessment will not be addressed in this scoping review.

Ethical Considerations

The scoping review will build upon previously published papers where data from potential trials have already been ethically approved before commencement, so no additional ethical approval is necessary.

Results

A preliminary search for potentially relevant articles was performed in April 2022 using the electronic databases IEEE Xplore, PubMed, Scopus, Google Scholar, National Center for Biotechnology Information, SAGE Journals, and ScienceDirect. A total of 4579 articles were found. The data extraction and analysis will be completed in early 2023. The qualitative and thematic analyses will be complemented by descriptive statistics and narrative form. We expect the results from this scoping review to be disseminated in a scientific peer-reviewed journal in 2023. The results will be disseminated through scientific conference presentations, oral presentations, and publication in a peer-reviewed journal.

Discussion

Expected Findings

In this scoping review protocol, we define interoperability in the context of IoMT and choose a 6-level model to conceptualize different interoperability issues that can arise during IoMT platform development. Additionally, we define a 5-level IoMT reference model to conceptualize building blocks of IoMT platforms. These definitions and building blocks will be the basis for our review, and data will be mapped to this structure.

From a clinical perspective, this scoping review will provide information necessary for building interoperable IoMT platforms for managing medical emergencies in home and prehospital care settings. To date, several reviews have been published regarding interoperability and IoMT platform development. However, to our knowledge, this will be the first review that combines interoperability and technologies with a focus on medical emergencies in prehospital and home care. The strengths of this study lie in the combination of an interoperability model and an IoMT reference model. By mapping interoperability issues to the layers in the IoMT model, we hope it will become clear how, where, and why different interoperability issues

appear. Furthermore, this study will include suitable technologies to overcome these concerns, which will facilitate readers to familiarize themselves with important tools needed to realize interoperable IoMT platforms.

Since we find collaboration between clinicians and engineers important in the context of IoMT development, our goal is to explain concepts in a simple way and continually point out application areas and how the technologies can be used to realize an IoMT platform. Another strength with the study is that readers with a nontechnical background should be able to comprehend the content and become acquainted with important concepts. The scoping review will be a facilitator for future interdisciplinary discussions.

Limitations

One limitation of this study is that because its focus is on technologies in IoMT settings, we have intentionally omitted articles covering technologies in other IoT settings. For example, IoT technologies predominated in automotive industry or Industry 4.0 will not be reviewed, even though they could potentially add value to the IoMT development process. Another limitation is that articles were collected from a limited set of literature resources from a specific time period and only those published in English. A limited search strategy can increase the risk of selection, retrieval, and publication bias. To reduce selection bias, however, the screening process will be performed by 2 reviewers.

Conclusions

This scoping review has the potential to influence future directions and may impact future IoMT platform developing processes. The results will elucidate important tools and concepts and enable clinicians and technicians to work closely in future development processes.

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Conflicts of Interest

OM is a sales engineer at InterSystems. There are no other conflicts of interest to declare.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 Checklist.
[PDF File (Adobe PDF File), 159 KB - resprot_v11i9e40243_app1.pdf]

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Abbreviations

AMQP: Advanced Message Queuing Protocol
APIs: application programming interfaces
ASAP: Acute Support, Assessment, and Prioritizing
CoAP: Constrained Application Protocol
EHR: electronic health record
EMS: emergency medical services
GDP: gross domestic product
IETF: Internet Engineering Task Force
IoMT: Internet of Medical Things
IoT: Internet of Things
MQTT: Message Queuing Telemetry Transport
OSI: Open Systems Interconnection
PMEAS: patient medical emergency alert system
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols
PSAP: public safety answering point
RFID: radio frequency identification
SDN: software-defined networking
WHO: World Health Organization

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Protocol

Psychometric Properties of the Hospital Anxiety and Depression Scale in Individuals With Chronic Obstructive Pulmonary Disease: Protocol for a Systematic Review

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Abstract

Background: In individuals with chronic obstructive pulmonary disease (COPD), anxiety and depression contribute to increased mortality and exacerbations, decreased physical functioning, and deteriorated health-related quality of life. The Hospital Anxiety and Depression Scale (HADS) is a patient-reported tool developed to measure symptoms of anxiety and depression in clinical settings. The HADS has been frequently used with individuals with COPD; however, its measurement properties lack critical appraisal in this population.

Objective: This review aims to summarize and critically appraise the validity, reliability, and responsiveness of the HADS in individuals with COPD.

Methods: Five electronic databases (MEDLINE, Embase, Scopus, PsychINFO, and Web of Science) will be systematically searched. Articles will be included if they assessed the measurement properties of the HADS in COPD; were published in a peer-reviewed journal; and were written in English. The COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) guidelines will be used to assess the methodological quality and level of evidence in the selected studies.

Results: To date, 12 articles met the inclusion criteria and will be included in the systematic review. The results of the psychometric properties of HADS will be qualitatively summarized and compared against the criteria for good measurement properties. The overall quality of evidence will be graded using the modified Grading of Recommendations, Assessment, Development and Evaluation approach. We expect to complete the systematic review by December 2022.

Conclusions: This systematic review will be the first to evaluate the psychometric properties of the HADS in individuals with COPD. Given the negative impact of anxiety and depression on physical functioning and health-related quality of life, this systematic review provides an opportunity to use the HADS as a validated measurement tool for the assessment and treatment of anxiety and depression in individuals with COPD.

Trial Registration: PROSPERO CRD42022302064; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=302064

International Registered Report Identifier (IRRID): PRR1-10.2196/37854

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KEYWORDS

COPD; HADS; reliability; responsiveness; validity; anxiety; depression; mental health; pulmonary; systematic review; protocol; mortality; functioning; quality of life; tool; symptoms; database

Introduction

Chronic obstructive pulmonary disease (COPD) is a common treatable but incurable lung disease that is characterized by persistent airflow limitation due to the significant exposure to noxious particles or gases resulting in a chronic inflammatory airway response [1]. COPD is strongly linked to a history of smoking and is associated with advanced age [2]. Globally, the World Health Organization estimates that COPD will be the third-leading cause of death in the world by 2030 [3].

Anxiety and depression are two of the most common and least treated comorbidities in individuals with COPD [4] with an estimated prevalence of 10% to 86% [4,5]. In general medical patients, anxiety disorders involve excessive feelings of fear, tension, and worry; changes in behavior such as avoidance or panic attacks; and physical manifestations such as tachycardia and hyperhidrosis [6]. Depressive disorders include emotions of sadness, loss of energy, anhedonia, and feelings of hopelessness, and can cause cognitive and somatic symptoms such as decreased appetite, fatigue, trouble sleeping, and difficulty concentrating [7].

Women and older adults (aged >65 years) with COPD are at an increased risk of developing both anxiety and depression [8,9]. Furthermore, individuals with COPD are 85% more likely to develop anxiety disorders than their healthy age-sex matched controls [10] and patients with other chronic diseases [11]. Anxiety is also reported to cause dyspnea at earlier stages of COPD [12,13], and both disorders are associated with decreased physical functioning and deteriorated health-related quality of life [14,15]. The assessment and timely interventions for these symptoms is essential, as anxiety and depression are associated with increased mortality, COPD exacerbations, hospitalizations [16,17], and medical costs [18].

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment tool developed to measure symptoms of anxiety and depression in clinical settings [19], and is used for individuals with COPD [20,21]. The scale consists of 14 items, with seven items assessing anxiety and seven items assessing depression. Items are rated on a 4-point Likert scale: zero (not present) to 3 (severe symptoms). Scores range from 0 to 21 for each subscale and can be summed to give a total anxiety-depression score with a maximum of 42 points. Higher scores indicate an increasing severity of symptoms, with a cutoff score of 8 indicating high symptoms of depression and anxiety [22].

Several systematic reviews examined the criterion validity of the HADS and reported a wide range of specificity (54%-95%) and sensitivity (44%-100%) values of the HADS in patients with mental disorders [23], impaired physical health [24], cancer [25], cardiac disease [26], multiple sclerosis [27], and COPD [28]. However, the methodological quality and level of evidence for criterion validity [28] and other measurement properties has not been evaluated and critically appraised for individuals with COPD.

We aim to evaluate and critically appraise the validity, reliability, and responsiveness of the HADS in individuals with COPD. Such an evaluation will provide robust measurement information for clinicians and researchers involved in respiratory care and guide the clinical assessment and management of anxiety and depression in individuals with COPD.

Methods

The systematic review will be conducted according to the COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) guidelines for systematic reviews [29], and the results will be reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [30]. The protocol registration number on PROSPERO is CRD42022302064.

Eligibility Criteria

Studies will be included if they assessed the psychometric properties (reliability, validity, responsiveness) of the HADS in adults 18 years and older who are diagnosed with COPD, are published in a peer-reviewed journal, and are written in the English language.

Studies will be excluded if they used the HADS as an outcome measure in an interventional study and did not assess its psychometric properties; included people younger than 18 years; assessed the psychometric properties of the HADS in patients with chronic disease other than COPD; included individuals with COPD during/immediately after acute exacerbations (within 4 weeks); and are systematic reviews, conference publications, abstracts, posters, editorials, and commentaries of the HADS.

Search Methods for Identification of Studies

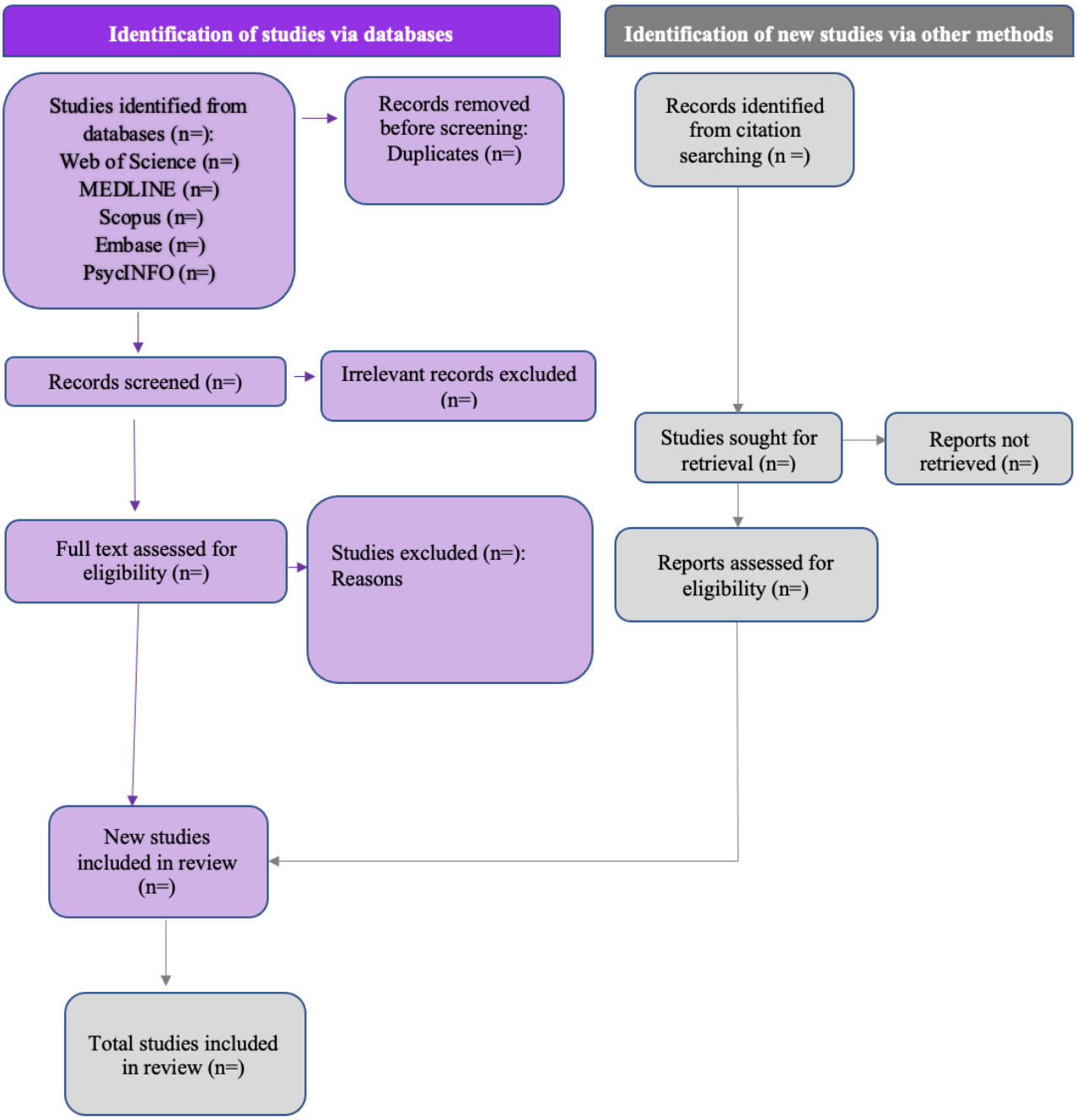
Two authors (AD and SQ) will independently conduct a systematic electronic search in five digital databases (MEDLINE, Embase, Scopus, PsychINFO, and Web of Science) from inception until March 2022 using the following keywords: reliability OR validity OR responsiveness OR psychometric properties OR measurement properties AND Hospital Anxiety and Depression Scale OR HADS AND Chronic Obstructive Pulmonary Disease OR COPD. In addition, the reference list of the selected studies will be manually searched to identify further relevant articles. Endnote (Clarivate) will be used to remove duplicates, and nonduplicated articles will be uploaded to Covidence for screening. An example of the search strategy in MEDLINE is reported in Multimedia Appendix 1.

Study Selection

Two authors (AD and EK) will independently perform screening of the titles and abstracts of the identified studies. Articles that appear to meet inclusion criteria will be included at this stage. These articles will be retrieved with full text and will be

screened independently by two reviewers. Disagreements between the two authors will be resolved by discussion with a senior research team member. An example of the PRISMA flow diagram showing the proposed study selection process for the HADS is presented in Figure 1.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram showing the proposed study selection process for the Hospital Anxiety and Depression Scale.



Data Extraction

Two authors (AN and EK) will independently carry out data extraction. The data extracted from individual studies will include the last name of the first author, year of publication, country, original language and available translations, study design, number of participants, age and sex of participants, and COPD severity. The HADS score and its psychometric properties including content, construct, criterion validity, reliability (internal consistency and measurement error), and responsiveness will also be extracted in accordance with COSMIN guidelines [29]. After completion, all data will be cross reviewed by the senior author for accuracy and completeness.

Methodological Quality

Two authors will independently evaluate the methodological quality of each selected study on psychometric properties using the COSMIN Risk of Bias checklist [29]. The results of the psychometric properties will be qualitatively summarized for all psychometric properties and compared against the criteria for good measurement properties to rate the overall summary

result of the scale as sufficient (+), insufficient (–), indeterminate (?), or inconsistent (±). A meta-analysis will be performed for the intraclass correlation coefficients if we find enough studies assessing test-retest reliability of the HADS in COPD. The overall quality of evidence will be graded as high, moderate, low, or very low using the modified Grading of Recommendations, Assessment, Development and Evaluation approach [29].

Hypothesis Testing for Construct and Criterion Validity and Responsiveness

To interpret the results of hypothesis testing and assess the quality of evidence for construct and criterion validity and responsiveness, the review team will formulate a set of hypotheses about the expected relationships (direction and magnitude) of the HADS and other instruments and variables based on COSMIN recommendations [29]. These hypotheses will be based on the literature and the clinical experiences of the review team. The review team expect strong correlations ($r \geq 0.50$) between the HADS and anxiety and depression scales (similar construct), moderate correlations ($0.30 \leq r < 0.50$) with related constructs such as positive affect, and weak or no correlations ($r < 0.30$) for unrelated constructs such as demographics. An example of the expected hypotheses is summarized in Multimedia Appendix 2.

Results

Five systematic databases will be searched for articles investigating the psychometric properties of the HADS. Currently, 12 articles met the inclusion criteria and are included in the systematic review. The results of the psychometric properties of the HADS will be qualitatively summarized and compared against the criteria for good measurement properties. The methodological quality of each selected study will be evaluated using the COSMIN Risk of Bias checklist [29]. The overall quality of evidence will be graded as high, moderate, low, or very low. We expect to complete the systematic review by December 2022.

Discussion

Anxiety and depression can negatively impact physical functioning, health-related quality of life, and adherence to pulmonary rehabilitation programs in individuals with COPD. This systematic review provides an opportunity to use the HADS as a validated measurement tool for the assessment and treatment of anxiety and depression in individuals with COPD in the clinical setting. This systematic review presents several strengths and limitations. It will be the first systematic review to evaluate and critically appraise the psychometric properties of the HADS in individuals with COPD. Additionally, a comprehensive literature search across five databases will be conducted. The limitations of this review include the possibility of excluding articles written in languages other than English and examining other chronic respiratory disorders.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search strategy.
[DOCX File , 15 KB - resprot_v11i9e37854_app1.docx]

Multimedia Appendix 2
Hypothesis testing for criterion and construct validity and responsiveness.
[DOCX File , 15 KB - resprot_v11i9e37854_app2.docx]

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Abbreviations

COPD: chronic obstructive pulmonary disease
COSMIN: Consensus-based Standards for the Selection of Health Measurement Instruments
HADS: Hospital Anxiety and Depression Scale
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Study of Health in Primary Care of the Amazonas Population: Protocol for an Observational Study on Diabetes Management in Brazil

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Abstract

Background: Changes in the profiles of patients have significant impacts on the health care system. Diabetes mellitus type 2 (T2DM) prevention and management should be studied in different contexts.

Objective: The Study of Health in Primary Care for the Amazonas Population (SAPPA) primarily aims to describe T2DM prevention and management actions offered by primary health care settings in Brazil and whether the care delivered is consistent with the chronic care model (CCM). Second, the study aims to examine the impact of T2DM management actions on health and lifestyle, and third, to understand how sociodemographic characteristics, health, and subjective outcomes impact diabetes management.

Methods: As part of this observational study, managers and health professionals complete a questionnaire containing information about T2DM prevention and management actions and CCM dimensions. During in-home visits, patients are asked about their health, lifestyle, sociodemographics, diabetes care, and subjective variables.

Results: A total of 34 managers, 1560 professional health workers, and 955 patients will be recruited. The data collection will be completed in October 2022.

Conclusions: The SAPPA is an observational study that intends to understand the T2DM management process in primary health care, including planning, execution, reach, and impact on patient motivation and adherence.

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KEYWORDS

health management; diabetes; patient activation; health care; T2DM; Amazon; patient profile; behavioral change; health policy; epidemiological profile; epidemiology; management

Introduction

The increase in life expectancy of the global population entails a growing demand for health care, due to increases in noncommunicable chronic diseases added to communicable diseases [1]. The transformation in the profile of patients means a new approach to health care [2]. However, there is a mismatch between the increase in chronic conditions and the management process, which still privileges acute conditions or the worsening of chronic conditions [3]. Any changes face barriers of verticality, immobilization, and fragmentation of the health system [4].

It has also been observed that health systems, in addition to having an essential role in the prevention of chronic diseases and in long-term health management strategies, must be developed alongside other sectors and community actors [5]. The care model adopted is crucial for the success of improving the living conditions of an individual or a community. In this case, the chronic care model (CCM) [6] is highlighted.

The CCM is based on the interaction between active and informed patients and health care teams that are proactive and prepared to meet the demands of the population under their responsibility. This model recommends that the highest care organization depends on key elements linked to the health care system, including health system/organizational support, clinical information systems, delivery system design, decision support, self-management support, and community resources [7].

Additionally, health care must consider institutional arrangements to meet populational, family, and individual demands, responding to specific contexts and respecting people's unique needs [6]. The macrolevel of health systems must also consider the microlevel of each patient, to optimize trajectories of intrinsic capacity [8]. There is evidence that focusing on the intrinsic capacity is more effective than prioritizing the treatment of specific chronic diseases [9,10]. This does not mean rejecting the treatment, but rather emphasizes that the preservation and recovery of people's physical and mental capacities must be objectives and starting points for health interventions. This proposition makes sense when we consider that people with strengthened physical and mental capacities will be better conditioned to respond to losses caused by the aging process and diseases. They may also respond better to rehabilitation or recovery processes in cases of injuries or acute illnesses [10].

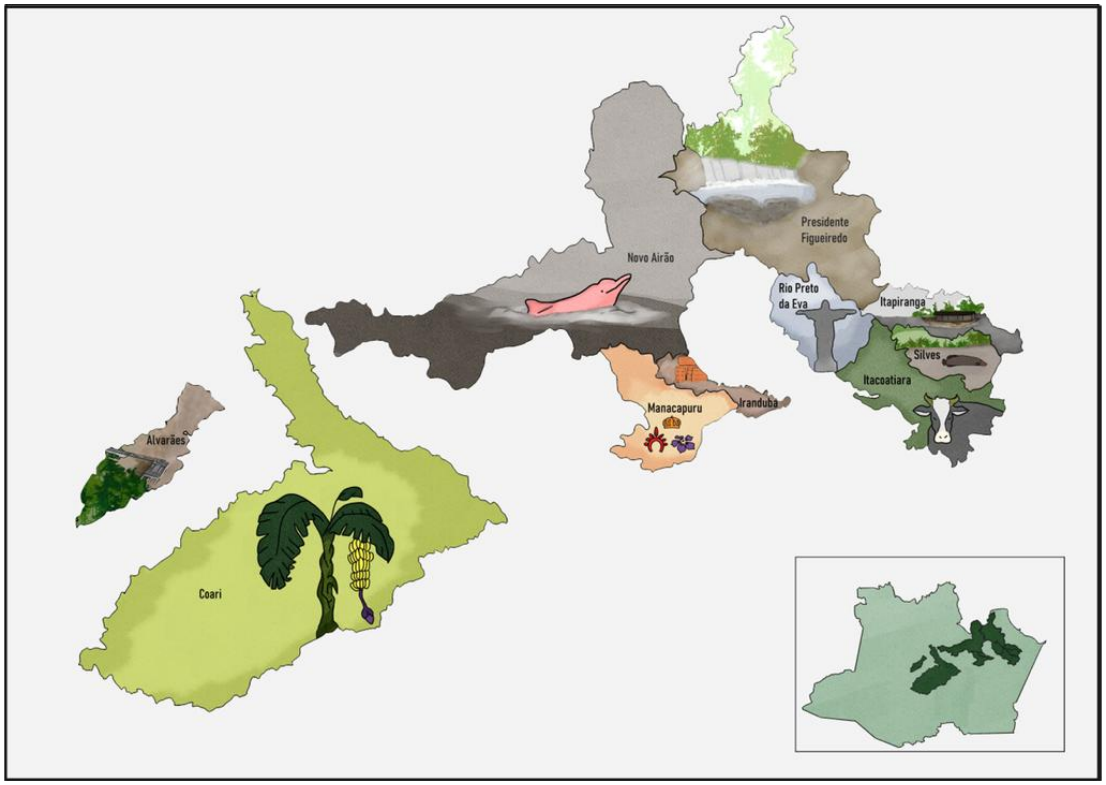
Understanding that different contexts can influence the care provided and received by the population leads to the need to search for evidence that supports the best planning of strategies. Therefore, the Study of Health in Primary Care of the Amazonas Population (SAPPA) is being conducted in the Amazonas Population. Three main aims motivated this research. The first aim is to describe management actions offered in primary health care settings in the State of Amazonas, Brazil, and whether the care delivered is consistent with the CCM. The second aim is to examine how this assistance addressed to patients with type 2 diabetes mellitus (T2DM) impacts health and lifestyle. The third aim is to better understand how sociodemographic characteristics, health, and diabetes and subjective variables could impact diabetes management.

Methods

Design Overview

The SAPPA is an observational study carried out on the population of Amazonas, Brazil. Data collection is being conducted in 2 Amazonas regions. The first region includes cities in the metropolitan region of Manaus. In 2010, this region had a degree of urbanization of 94% and approximately 60% of the state population resided in this area [11]. The metropolitan region of Manaus includes Iranduba (38.1 km by car from the capital), Itacoatiara (270 km by car from the capital), Manacapuru (98.8 km by car from the capital), Novo Ayrão (194.8 km by car from the capital), Presidente Figueiredo (125.5 km by car from the capital), Rio Preto da Eva (80.2 km by car from the capital), Silves (267 km by car from the capital), and Itapiranga (339.1 km by car from the capital). The second region of SAPPA includes cities located at Medium Solimões: Coari (363 km by boat from the capital) and Alvarães (532 km by boat from the capital; Figure 1).

Figure 1. Amazonas cities.



Setting

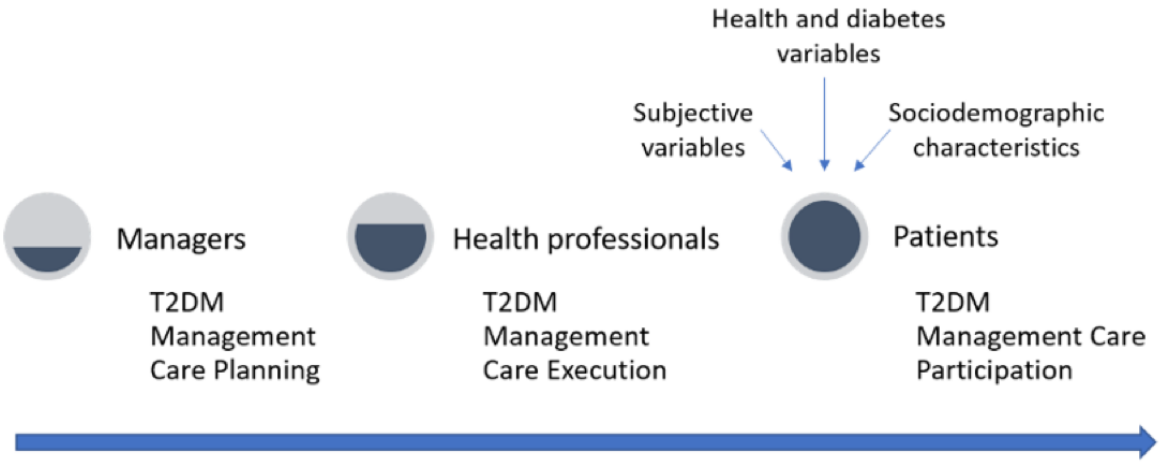
Briefly, the Brazilian health system is elaborated from a set of institutional environments between the 3 spheres of management (union, states, and cities). This approach aims to promote innovations in management processes and instruments, proposing to achieve greater efficiency and quality in the responses of the unified health system [12].

In this process, the Health Ministry (federal government) is responsible for proposing policies; participating in the financing, technical cooperation, evaluation, regulation, control, and inspection of health care; and medication supply [13].

For T2DM, preventive and health promotion measures are integrated, including support for the prevention of complications, diagnosis of cases, treatment and follow-up, emergency care, and case referral. However, the responsibility for coordinating and planning actions based on the recommendations for the prevention and management of T2DM is held in primary health care settings [14].

At the municipal level, the primary health care manager and health professionals are required to define the actions and services that should be developed in their settings and build the care flows that must be guaranteed to the patients in order to attend to patients' health needs [14]. In this way, primary health care settings play a central role in the T2DM management process (Figure 2).

Figure 2. Diabetes management process in primary health care settings. T2DM: Diabetes mellitus type 2.



Participant Eligibility and Recruitment

The SAPPA is being conducted in primary health care units in each city, including urban and rural areas, according to the National Register of Health Establishments. Selection takes place randomly by drawing lots, and all units have the same chance of being drawn. Recruitment of participants started in August 2020, and the data collection is intended to be completed in October 2022.

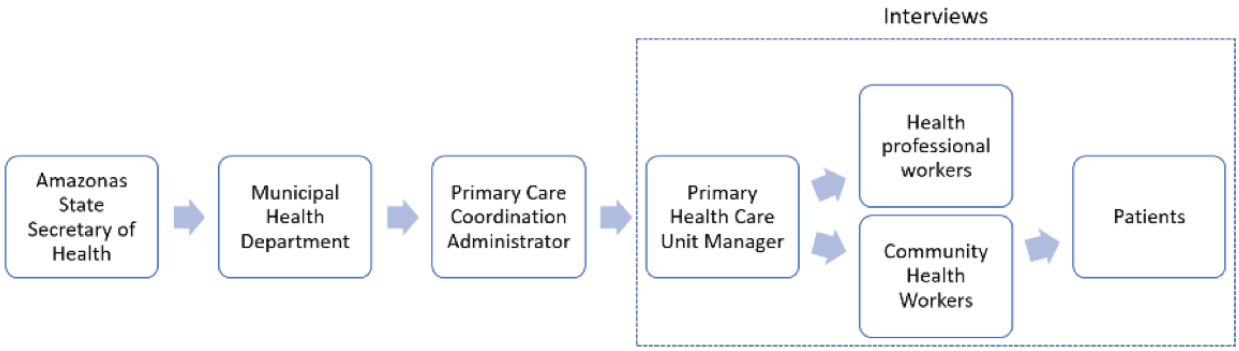
Figure 3 describes the process for engaging cities and administrators in the study and recruitment. Briefly, initially, the Amazonas State Secretary of Health was contacted for approval. Following this approval, each municipal health department was contacted to engage administrators and managers. After agreement from the municipal health department to participate in the study, the primary health care coordination administrators for each municipality were contacted. These coordinators facilitate contact with managers from each primary health care unit. An individual member from the SAPPA contacts the primary health care unit managers by phone to schedule the site visit for data collection. During the site visit, the project proposal and the field team are presented to the community health workers to establish the partnership. The community health workers provide patients' names and addresses and accompany the field team during home visits.

Inclusion criteria for managers: All managers from primary health care units are invited to participate and are interviewed in private in their offices.

Inclusion criteria for professional health workers: professional health workers who have been involved in patient assistance for at least 3 months, including nurses, health technicians, physicians, community health workers, physical educational professionals, physiotherapists, dieticians, and dentists are invited to participate in the study. Inclusion criteria for patients: patients with a T2DM diagnosis and in primary health care for at least 6 months.

Exclusion criteria for professional health workers: professional health workers who are on vacation or sick leave. Exclusion criteria for patients: patients who present a communication disorder that makes it unfeasible to collect data.

Figure 3. Consent and recruitment process.



Sample Size Calculation

Considering the total number of 142 health units distributed in urban and rural areas in 10 cities, and setting the margin of error at 15% and the confidence level at 95%, a sample of 34 units was obtained. Proportional stratified sampling was used for the estimated number of interviews per city. The distribution of the sample is detailed in Table 1. The choice of individuals and urban and rural units for collection was made using the simple random sampling method.

The SAPPA sampling design was based on the Continuous National Household Sample Survey, used to estimate the total number of the study population, thus satisfying the sampling proportionalities within each stratum. The target population was formed by patients with DM2 registered in primary health care in each city. The estimated number of T2DM patients was obtained considering the prevalence of diabetes of 5.2% [15]. This sample size was calculated for each city and allows a confidence level of 99% and a margin of error of 10%.

Table 1. Sample distribution.

City and location	Total primary health care units	Selected primary health care units	Patient interview calculation
Iranduba			
Rural	5	1	26
Urban	15	3	78
Itacoatiara			
Rural	9	2	146
Urban	7	1	73
Itapiranga			
Urban	5	1	20
Manacapuru			
Rural	9	2	84
Urban	12	3	126
Novo Airão			
Rural	5	1	21
Urban	5	1	21
Presidente Figueiredo			
Rural	14	3	47
Urban	9	2	31
Rio Preto da Eva			
Rural	10	2	48
Urban	5	1	24
Silves			
Rural	8	1	20
Urban	2	0	0
Alvarães			
Rural	3	1	18
Urban	4	2	16
Coari			
Urban	15	7	156
Total	142	34	955

Data Collection Procedures

The field team is composed of 30 interviewers and 2 supervisors. The supervisors are part of the coordination team, and the interviewers are undergraduate students from the Health College (Nursing and Physical Therapy College). The field team was carefully trained before the start of the study by repeatedly applying SAPPA forms. Three interviewers were trained to exclusively apply the forms to managers and health workers. The other interviewers were trained to apply the forms to patients. Videos were specially produced for the training of anthropometric and functional capacity measurements. The field team training takes approximately 3 hours. To ensure the same measurement standards and practices, after training the interviewers conduct a mock session under staff supervision. A series of checks are conducted regularly to identify outliers and discrepancies in measurements. Appropriate measures are taken whenever problems are detected. If necessary, field team members are retrained, and equipment is constantly checked and replaced.

Data collection in cities in the metropolitan region of Manaus is performed in a round site visit. The field team for each visit includes 1 supervisor, 3 manager/health worker interviewers, and at least 12 patient interviewers. On a previously scheduled date, the field team leaves Manaus for the target cities using the transport from the University and carrying all the data collection equipment.

Upon arriving at the primary health care units, the supervisor introduces themself to the manager and presents the project proposal and field team to the professional health workers. The manager/professional interviewer remains at the primary health care unit for the interviews, while the other interviewers and

the supervisor accompany the community health workers on home visits. At the patient residence, the interviewers are introduced to the patients by the community health workers and invite the patients to join the research.

After the patient agrees to participate in the research, data collection begins. The patient forms and evaluations are applied in the home by the field team, and take an average of 1 hour to complete. For the Medium Solimões data collection, a local field team was formed, including 1 supervisor, 2 manager/professional interviewers, and 12 patient interviewers. After training, the same data collection procedure was adopted.

Instruments

Table 2 describes the variables included in the SAPPA data collection.

Table 2. Instruments for data collection.

Participants	
Managers	
	• Development and execution of actions for the prevention and management of T2DM[a]
Professional health workers	
	• Participation in actions for the prevention and management of T2DM • Assistance of the organization with respect to T2DM evaluation
Patients	
Sociodemographic characteristics	• Sex, age, marital status, skin color, educational level, employment status, monthly income, number of household members, and religion
Health-related variables	• Self-perceived health • Memory and cognition • Patient engagement • Disease burden • Medications and drug use (including antidiabetic drugs and insulin) • Frequency of consumption of medicinal plants • Pain
Physical frailty	• Physical functional capacity • Frailty • Sarcopenia • T2DM diagnosis time
Diabetes variables	• Participation in actions focused on diabetes management • Nutritional behavior • Quality of care
Behavioral variables	• Physical activity level and sedentary behavior • Tobacco and alcohol consumption • Insomnia and daytime sleep
Subjective health assessment	• Intrinsic religiosity • Life purpose • Overall life satisfaction
Anthropometric measurements	• Height, weight, and BMI

[a]T2DM: type 2 diabetes mellitus.

Manager Instruments

Managers are invited to complete a form containing information about T2DM prevention and management actions already implemented in the primary health care units. These forms are applied during the on-site visits by a field researcher using an Android device.

To identify actions taken to manage T2DM in primary health care in the State of Amazonas, the managers are asked to complete a questionnaire describing the development of prevention and management of T2DM actions, scope of the actions, cost of implementation and professionals involved, effectiveness, and maintenance of the actions [16].

Professional Health Worker Instruments

Professional health workers are interviewed by a field researcher in the primary health care settings. They are invited to respond to questions about their participation in actions related to the prevention and management of T2DM [16]. They then complete the questionnaire for the Assessment of Chronic Illness Care (ACIC).

To assess and monitor health care systems, researchers from the McColl Institute for Health Care Innovation [17] proposed 2 instruments: the ACIC and the Patient Assessment of Chronic Illness Care. The ACIC provides guidance for professional health workers in order to assess their perception of the care provided by their setting for T2DM chronic conditions.

The ACIC is composed of 6 dimensions associated with the realization of the CCM, and a seventh, which assesses the integration of the dimensions. The perceptions obtained are analyzed using a scoring scale, from 0 to 11, where 0 represents the lowest score, that is, a place with very limited resources and structures and 11, the highest score, indicating a place with good resources and an optimal structure for the care of chronic conditions. The 7 dimensions of the ACIC instrument are made up of the organization of health care, interaction with the community, supported self-care, decision support, design of the delivery system service, clinical information system, and integration of CCM components [18].

Patient Instruments

The patient is interviewed at home, through a form completed by a field researcher using an Android device. The following variables are collected:

Sociodemographic variables include sex, age, race/ethnicity, marital status, educational level, employment status, monthly income, number of household members, and religion.

Health-related variables included cognitive status, self-perceived health, disease burden, medications, consumption of medicinal plants, patient engagement, and pain.

- Cognitive assessment is addressed through the 10-point Cognitive Screener [19] and Figure Recognition Test [20], a brief and easy-to-use screening strategy with higher accuracy developed for the Brazilian population [19], presenting sensitivity of 60.5 and specificity of 94.3 [21].
- Self-perceived health is obtained through questions such as, “In general, how do you assess your health at present?” “How do you rate your health compared to other people your age?” “How do you rate your memory compared to other people your age?” “How do you rate your health today compared to 1 year ago?” and “How do you rate your activity today, compared to a year ago?” Possible responses were much worse, worse, equal, better, much better, and no answer [22].
- Disease burden is measured by the Functional Comorbidity Index which consists of a list of 18 comorbidities. The score is obtained by the sum of all comorbidities present and ranges from 0 to 18 [23].
- The number of medications and medication adherence is collected through the registration of all medications prescribed in the last medical appointment. In addition, participants are asked how many days of medication doses were missed in the previous 7 days [24].
- The consumption of medicinal plants is measured by type and frequency.
- Patient engagement is a construct that includes self-efficacy, behavior, and knowledge, and has been shown to predict a variety of health behaviors [25]. The Patient Activation Measure -13 (PAM-13) was applied, which includes measurements of the use of self-management services, the performance of self-management behaviors, and medication adherence [25]. The PAM-13 is a 13-item measure that assesses self-efficacy, behavior, and knowledge [25]. Item scores range from 0 to 4, with 0=not applicable, 1=strongly disagree, 2=disagree, 3=agree, and 4=strongly agree. Mean PAM-13 scores are then transformed into a score ranging from 0 to 100, where higher scores represent higher activation. PAM-13 scores are assigned to 1 of the 4 stages of activation, based on the Insignia Health guidelines. PAM level 1 refers to very low activation (0-47 points) meaning disengaged and overwhelmed; level 2 (47,1-55,1), becoming aware but still struggling; level 3 (55.2-67.0), taking action; and level 4, high activation (67-100), meaning maintaining behaviors and pushing further [26]. This measurement was validated for the Brazilian population [27].
- The presence of pain and intensity was measured using the visual analog scale and Faces Pain Scale, which allows the quantification of pain intensity using numbers on a scale from 0 to 10, where 0 indicates the minimum pain and 10 indicates the maximum pain possible [28]. The Face Scale indicates the intensity of pain according to the mimicry represented on each drawn face, with the expression of happiness corresponding to the classification no pain and the expression of maximum sadness corresponding to the classification maximum pain [29].

Diabetes variables: T2DM diagnosis time, use of antidiabetic drugs or insulin, active participation in activities focused on diabetes prevention and management offered by primary health care and partners [16], and quality of care.

- Quality of care is measured by the Patient Assessment of Chronic Illness Care instrument, congruent with the CCM, whereby patients report their experiences of the care delivery system. The survey includes 20 items and is sufficiently brief to use in many settings [30]. When paired with the ACIC, these tools can provide complementary consumer and provider assessments of important aspects of care for patients with chronic illness [31]. The survey was validated for the Brazilian population [18]. Respondents answer each item with a response from 1=almost never to 5=almost always. For scoring: patient activation: average of items 1-3, delivery system: average of items 4-6, goal-setting: average of items 7-11, problem solving: average of items 12-15, and follow-up: average of items 16-20 [31].

Physical frailty: functional capacity, daily and instrumental activities of daily living, sarcopenia, and frailty.

- Short Physical Performance Battery Test is used to assess functional capacity, through the following domains: gait speed at a normal pace, static balance in an orthostatic position, and strength of the lower limbs through observation if the participant can get up and sit in a chair. Total scores are calculated by summing the 3 individual test items, with a potential range of 0-12 points. Higher scores indicate better lower body function [32], presenting a sensitivity of 79.7 and specificity of 73.8 [33].

- Brazilian version of the Older Americans Resources and Services Multidimensional Functional Assessment Questionnaire assesses the difficulty reported in performing 15 daily living and 7 instrumental activities of daily living. The total number of activities of daily living that the patient reports difficulty in performing is quantified, that is, the total number of activities compromised. The higher the score, the greater the impairment in functional capacity [34]. The tool presents sensitivity of 83 and specificity of 69 [35].
- The risk of sarcopenia is identified through the Strength, Ambulation, Rising from a Chair, Stair Climbing, and History of Falling questionnaire: muscle strength, the need for assistance with walking, ability to get up from a chair and climb stairs, and frequency of falls. The score given to each item is from 0 to 2 points, reaching the sum of 0 to 10 points. Patients who present a result greater than or equal to 4 in this questionnaire are classified as at risk of sarcopenia [36]. The circumference calf measurement is also included [37]. The tool presents sensitivity of 60 and specificity of 80.92 [38].
- Frailty will be addressed according to the Fried criteria [39]. These criteria include 5 components: (a) unintentional weight loss of ≥4.5 kg in the last year (obtained from the patient), (b) weakness (assessed using the hand-grip strength measurement; considering the interpretation of results based on sex and BMI), (c) exhaustion (evaluated based on 2 questions from the Center for Epidemiological Studies Depression scale [40]), (d) slow gait (walking time over a distance of 4 meters; interpretation of results takes into account sex and height), (e) low physical activity (weekly energy expenditure rate calculated based on International Physical Activity Questionnaire [IPAQ] [41]). An Instrutherm@ digital dynamometer is used for the hand-grip strength measurement.
- The Clinical-Functional Vulnerability Index–20 is used as a 20-item instrument for screening frailty developed by a Brazilian team that assess self-perception of health, activities of daily living, cognition, mood, mobility, communication, and multiple comorbidities, resulting in a classification based on the score achieved as follows: robust older adult when the score is 0 to 6, older adults at risk of frailty with a score between 7 and 14, and frail older adults when the score is greater than or equal to 15 [42]. The tool presents sensitivity of 90.5 and specificity of 71 [43].

Behavioral variables: nutritional behaviors, physical activity behaviors, tobacco and alcohol consumption, insomnia, and daytime sleep.

- Nutritional behavior (regular consumption of fruits and vegetables and fish).
- Physical activity behaviors: physical activity is measured using the short version of the IPAQ, validated for the Brazilian population [41]. Duration (minutes) and frequency (days) of physical activity in the previous 7 days is measured in the following domains: job-related, transportation, housework, house maintenance, caring for family, recreation, sport and leisure time, and time spent sitting. These activity categories are treated separately to obtain the specific activity patterns or multiplied by their estimated value in metabolic equivalent of tasks (METs) and summed to gain an overall estimate of physical activity in a week. The MET intensity values used to score IPAQ questions in this study are vigorous (8 METs), moderate (4 METs), and walking (3.3 METs) [44]. The IPAQ sitting question (2 questions) are indicators of the time spent in sedentary activity and not included as part of the summary score of total physical activity [41,45]. The IPAQ demonstrates sensitivity of 81 and specificity of 85 [46].
- Lifetime tobacco use is obtained through self-report with the question: “Do you have or did you have the habit of smoking?” (nonsmoker, ex-smoker, and current smoker) and “How long have you been a smoker?” [22].
- Alcohol consumption patterns are addressed by these questions: frequency of consumption (never drink alcoholic beverages; drink once a month; drink once a week; daily binge drinking) and amount ingested. High intake is defined as more than 5 units (bottle/can/dose/cup) on the same day [47].
- Insomnia and daytime sleep: questions were extracted from the Nottingham health profile and validated for use in Brazil [48]. The question on duration of daytime naps in the previous 12 months was taken from the Minnesota Leisure Activity Questionnaire [49].

Subjective assessment: intrinsic religiousness, life purpose, and overall life satisfaction.

- A brief measure of intrinsic religiousness, namely the Intrinsic Religiousness Inventory [50], a valid instrument to measure the impact of religion on physical and mental health in Brazilian samples [50,51], is applied. It consists of a structured questionnaire, which is organized on a Likert scale, with scores ranging from 1 to 5 that reflect gradations of intensity/frequency: 1=never, 2=rarely, 3=occasionally, 4=often, and 5=always. The initial version of the Intrinsic Religiousness Inventory was developed from the compilation of statements with themes related to the construct of intrinsic religiosity, based on a literature review and suggestions from specialists [50].
- The Brazilian version of the Life Purpose Scale is a 10-item self-report measure and was semantically and culturally validated for use with the Brazilian population [52].
- Overall life satisfaction questions: “Are you satisfied with: your life? Your health? Your memory to do and remember daily things? Your friendships and family relationships? The environment (climate, noise, pollution, attractions, and safety)?”

Anthropometric measurements: height, weight, and BMI.

- Height is measured to the nearest 1 mm using a tape measure with the participant in a full standing position (in the Frankfort horizontal plane). Patients are asked to wear light clothing and no shoes and the average of 2 measurements is considered.
- Weight is measured using a digital scale (model Digital Glass 7 FW, G-TECH) and the average of 2 measurements is considered.

- BMI is calculated from weight (kg) divided by the square of height (m).

Data Collection Tools

The first step of the SAPPA data collection is the selection and preparation of the questionnaires included in each form: managers, professional health workers, and patients.

The forms for managers and health workers were created using a mobile-based data collection tool designed by KoBoToolbox (Kobo Inc). The field team carries an Android device during the interviews. The Android device (phone or tablet) is embedded with KoBoCollect and allows the forms to be constructed and reviewed entirely offline, as well as allowing data collection offline. The information system requires internet access and is performed by downloading the SAPPA questionnaire from the mobile-based data collection.

KoBoCollect is a data collection Android app based on an open data kit (ODK) that can be installed on any standard Android device (phone or tablet). The form captures the data and securely transmits it to the central server via Wi-Fi. Other alternative data transfer methods include mobile phone networks or a direct cable. One of the major advantages of the SAPPA information system is that all data are immediately available after data collection. Data storage and management are centralized at the Federal University of Amazonas using a cloud service.

The patient form was also built on ODK as previously described. To create a data collection flow during the home visit to the patient, the questions are grouped by categories: (1) sociodemographic variables, (2) cognitive evaluation, (3) religiousness, (4) health-related variables, (5) diabetes variables, (6) medications and medicinal plants, (7) pain, (8) behavior variables, (9) functional activities, (10) emotional aspects, (11) relationship, and (12) functional evaluation. The SAPPA questionnaire was built using a mobile-based data collection tool designed by KoBoToolbox.

Ethics Approval

The SAPPA was approved by the Federal University of Amazonas ethics board (4.318.325 and 4.994.196), and the study was performed following approved guidelines and the Declaration of Helsinki. All participants are required to sign informed consent forms prior to interviews (managers, health workers, and patients), physical measurements (patients), and photo registry (patients).

Study findings will be disseminated through scientific conferences, peer-reviewed journal publications, and invited lectures. Results from this study will be reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and submitted for peer-reviewed publications.

Statistical Analysis

Data will be analyzed using SPSS (version 20.0, IBM Corp). Unless otherwise specified, a significance level of $P<.05$ will be adopted in all statistical analyses. Sample and subsample characteristics will be presented using frequencies for categorical variables and mean and standard deviation for continuous variables. Multiple linear (continuous dependent variable) and logistic (binomial dependent variable) regression analyses will be used to study the association between the independent and dependent variables of interest. Other analyses may be applied and will be reported in future papers.

Results

A total of 34 managers, 1560 professional health workers, and 955 patients will be recruited. The data collection is intended to be completed in October 2022.

Discussion

We present the design of the ongoing SAPPA Study. The goal of the study is not only to build an understanding of the current T2DM management provided to the Amazonas population but also to provide scientific data to support policy changes that may affect and improve patient assistance. Identifying the current management process could allow us to propose a new approach for this unique population based on the SAPPA findings.

Cities in Amazonas are particular in several aspects when compared to other cities in Brazil. This is the case in the metropolitan region of Manaus, which has a peculiar spatiality composed of a large territorial extension with significant population gaps between its urban centers. Apart from Manaus, the other cities included have the characteristic of being responsible for supplying agricultural products and labor for the capital [53]. These cities, despite being close to the capital, have a much lower degree of development and great economic and social fragility, due to the scarcity of income-generating agents and the ease of migration. This situation is aggravated by moving away from the urban perimeter of these cities toward the various rural communities that are located on the riverbanks or roads and neighboring areas. In these places, access to goods and services becomes very difficult, expectations decrease, and social risks increase [54]. These inequalities reflect in the care conditions for the population, affecting the quality of care and life available for patients and assisted families [54].

Despite continuous investments, the findings of the study proposed by Silva et al [55] show a social scene that is ineffective for the health demands of the Amazonas population. The study demonstrates a predominance of asymmetry, verticality, competitiveness, and fragility in the assistance provided. Political agents involved in the process have limited understanding of the sociopolitical and institutional conditions in which they operate. They tend to attribute the management and operationalization problems of assistance networks to the configuration of Amazonian natural geographic spaces, but their financing, governance, and technical capacity are insufficient to overcome these problems [55].

The persistent absence of a care design capable of guaranteeing the referral of patients in the health region perpetuates an informal flow in which situations are resolved on a case-by-case basis, without a definition of priorities and a cost-effectiveness analysis to properly direct the resolution. The lack of discussions and agreements aimed at instituting care networks explain, to

some extent, the persistence of a notary management model, with little adherence to the concrete needs of patients [55].

Only the evaluation and identification of priorities, which enables the construction of a health care model focused on primary health care that can also cope with chronic diseases and conditions, will allow innovation in care. This, in turn, will allow the implementation of new care strategies, whether individual or collective, and the transformation of health care in this region.

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Data Availability

The data that support the findings of this study will be available on request from the corresponding author, EBL. The data will not be publicly available due to personal identification restrictions that could compromise the privacy of research participants.

Authors' Contributions

EBL and HLMC were responsible for conception, data collection, and manuscript writing. FAB and FAA were responsible for conception and manuscript reviewing. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Conflicts of Interest

None declared.

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Abbreviations

ACIC: Assessment of Chronic Illness Care
CCM: chronic care model
IPAQ: International Physical Activity Questionnaire
MET: metabolic equivalent of task
ODK: open data kit

SAPPA: Study of Health in Primary Care for the Amazonas Population
STROBE: strengthening the reporting of observational studies in epidemiology
T2DM: type 2 diabetes mellitus

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Protocol

Neurorehabilitation Through Synergistic Man-Machine Interfaces Promoting Dormant Neuroplasticity in Spinal Cord Injury: Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: Spinal cord injury (SCI) constitutes a major sociomedical problem, impacting approximately 0.32-0.64 million people each year worldwide; particularly, it impacts young individuals, causing long-term, often irreversible disability. While effective rehabilitation of patients with SCI remains a significant challenge, novel neural engineering technologies have emerged to target and promote dormant neuroplasticity in the central nervous system.

Objective: This study aims to develop, pilot test, and optimize a platform based on multiple immersive man-machine interfaces offering rich feedback, including (1) visual motor imagery training under high-density electroencephalographic recording, (2) mountable robotic arms controlled with a wireless brain-computer interface (BCI), (3) a body-machine interface (BMI) consisting of wearable robotics jacket and gloves in combination with a serious game (SG) application, and (4) an augmented reality module. The platform will be used to validate a self-paced neurorehabilitation intervention and to study cortical activity in chronic complete and incomplete SCI at the cervical spine.

Methods: A 3-phase pilot study (clinical trial) was designed to evaluate the NeuroSuitUp platform, including patients with chronic cervical SCI with complete and incomplete injury aged over 14 years and age-/sex-matched healthy participants. Outcome measures include BCI control and performance in the BMI-SG module, as well as improvement of functional independence, while also monitoring neuropsychological parameters such as kinesthetic imagery, motivation, self-esteem, depression and anxiety, mental effort, discomfort, and perception of robotics. Participant enrollment into the main clinical trial is estimated to begin in January 2023 and end by December 2023.

Results: A preliminary analysis of collected data during pilot testing of BMI-SG by healthy participants showed that the platform was easy to use, caused no discomfort, and the robotics were perceived positively by the participants. Analysis of results from the main clinical trial will begin as recruitment progresses and findings from the complete analysis of results are expected in early 2024.

Conclusions: Chronic SCI is characterized by irreversible disability impacting functional independence. NeuroSuitUp could provide a valuable complementary platform for training in immersive rehabilitation methods to promote dormant neural plasticity.

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International Registered Report Identifier (IRRID): PRR1-10.2196/41152

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KEYWORDS

body-machine interface; brain-computer interface; neural rehabilitation; serious games; spinal cord injury; wearable robotics

Introduction

Spinal cord injury (SCI) constitutes a major sociomedical problem, impacting approximately 0.32-0.64 million people each year worldwide; particularly, it impacts young individuals, causing long-term, often irreversible disability [1]. The sensorimotor networks of patients with SCI and healthy individuals share similar connectivity patterns, but new functional interactions have been identified as unique to the sensorimotor networks of patients with SCI [2-4] and can be attributed to both adaptive and maladaptive organization effects after the injury. The importance of such phenomena both as possible prognostic factors and as contributors to patient rehabilitation remains unspecified as of yet. The exact underlying neurophysiological process and the extent to which this is modulated by higher-order interactions are also not fully understood [5]. By contrast, researchers have recently demonstrated for the first time partial neurological recovery 5-10 years after complete SCI through groundbreaking neurorehabilitation protocols [6]. The investigators used rich visual and tactile feedback, virtual reality environments, a brain-computer interface (BCI)–controlled exoskeleton, and robotic actuators, as well as documented plasticity effects at the cortical level to support their theory [6-8]. The authors found that patients experienced integration of virtual legs into their body schema and proceeded to develop a multistage neurorehabilitation protocol for patients with chronic SCI. While the original aim was to explore a long-term body-machine interface (BMI)–based protocol for patients with SCI that helps them regain the ability to walk autonomously using brain-controlled exoskeletons, unexpectedly patients with chronic SCI experienced a significant clinical improvement in their ability to perceive somatic sensations and exert voluntary motor control in dermatomes located below the injury. An electroencephalography (EEG) analysis revealed clear signs of cortical functional plasticity, suggesting, for the first time, that such long-term multimodal training may induce sensorimotor plasticity capable of triggering partial neurological recovery [9,10]. The importance of proper control scheme design in targeting neural plasticity during neural rehabilitation has also been demonstrated by invasive interfaces, such as spinal cord stimulation below the injury level, where novel findings suggest that reproducing natural central nervous system (CNS) input and output patterns below the injury level can lead to long-term functional improvement, even without stimulation, for select patients with chronic SCI [11].

Residual communication between brain and spinal cord plays an important role in possible neurorehabilitation, as even in complete injuries one-fourth of nerve fibers crossing the injury level are functionally intact. As such, retraining CNS circuits and promoting plasticity to restore body functions have been recognized among key principles of spinal cord repair by the US National Institute of Neurological Disorders and Stroke (US NIH/NINDS). Nonetheless, existing literature does not yet portray with precision the pathophysiological process and effect of SCI on CNS and the sensorimotor networks [2,12-14]. Studies needed to address this issue should consider identifying specific questions to be answered through further investigation: (1) how and why reorganization of CNS networks are established, (2) how this reorganization evolves in time with respect to the severity and chronicity of the injury, (3) when can it be considered an adaptive or maladaptive evolution, and (4) how can it be promoted or prevented, respectively. The insight gained is expected to hold clinical relevance in preventing maladaptive plasticity after SCI through individualized neurorehabilitation, as well as in the design of assistive technologies for patients with SCI. While new assistive technologies, including robotics and spinal cord stimulation, have emerged as potential methods to replace lost mobility [15], it has been demonstrated that SCI impacts the whole CNS, inducing adaptive and maladaptive neuroplasticity. Multiple training modalities, immersive environments, and rich and versatile feedback (visual and tactile) in neurorehabilitation have demonstrated the ability to promote neural plasticity and induce partial neurological recovery in paraplegia even after chronic complete SCI.

The main hypothesis for the NeuroSuitUp clinical trial suggests that patients with chronic upper SCI can benefit from training in multiple man-machine modalities and present neurological improvements due to synergistically induced neuroplasticity. As such, the objective of NeuroSuitUp is to develop, pilot test, and optimize a platform based on multiple immersive man-machine interfaces offering rich feedback that include (1) visual motor imagery (VMI) training under high-density EEG recording, (2) mountable robotic arms controlled with wireless BCI, (3) a BMI consisting of wearable robotics jacket and gloves in combination with a serious game (SG) application and rich audiovisual stimuli, and (4) an augmented reality (AR) module.

The platform will be used to validate a self-paced neurorehabilitation intervention and to study cortical activity in chronic complete and incomplete SCIs at the cervical spine.

Methods

The components of the NeuroSuitUp platform, the protocol used for patient recruitment, the experimental procedures for the pilot testing, and the questionnaires and outcomes used in the study are described hereby.

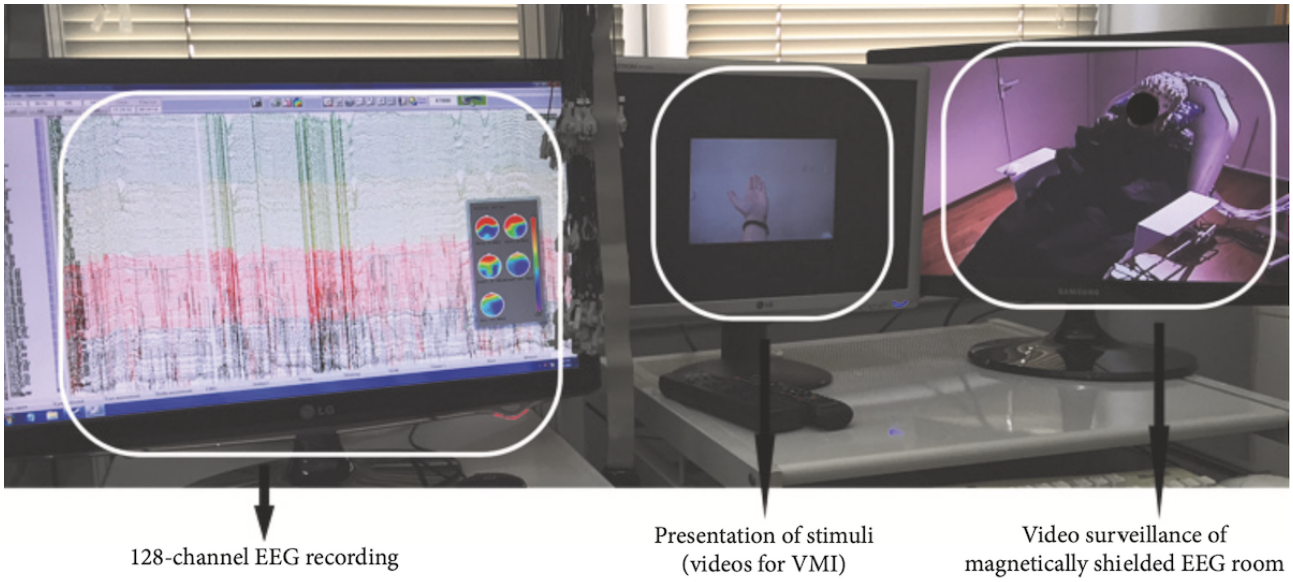
Overview of the NeuroSuitUp platform

The main components of the NeuroSuitUp platform have been selected to assemble an immersive platform consisting of multiple man-machine interfaces that present synergies in their use and implementation. The components consist of the following: (1) VMI training under high-density EEG recording, (2) mountable robotic arms controlled with wireless BCI, (3) BMI consisting of wearable robotics jacket and gloves in combination with an SG application, and (4) an AR module.

Visual Motor Imagery Under High-Density Electroencephalography

Participants during the 3 main sessions (initial, intermediate, final) will train their VMI by attempting multiple imaginary movements of the upper limbs (32 possible movements of the right and left upper extremities), and during walking imagery, while under high-density EEG recording (128 channels). The participants will watch age- and sex-matched upper limbs in a screen performing these motions while attempting to imagine that these are their own arms performing the movement. The torso and arms of the participants will be covered by a black sheet to facilitate registration of the presented extremities into their own body schema (Figure 1). This experimental setup has already been tested by the authors with patients with SCI to train motor-related imagery and pretrain mental strategies for kinesthetic BCI classification [3,4].

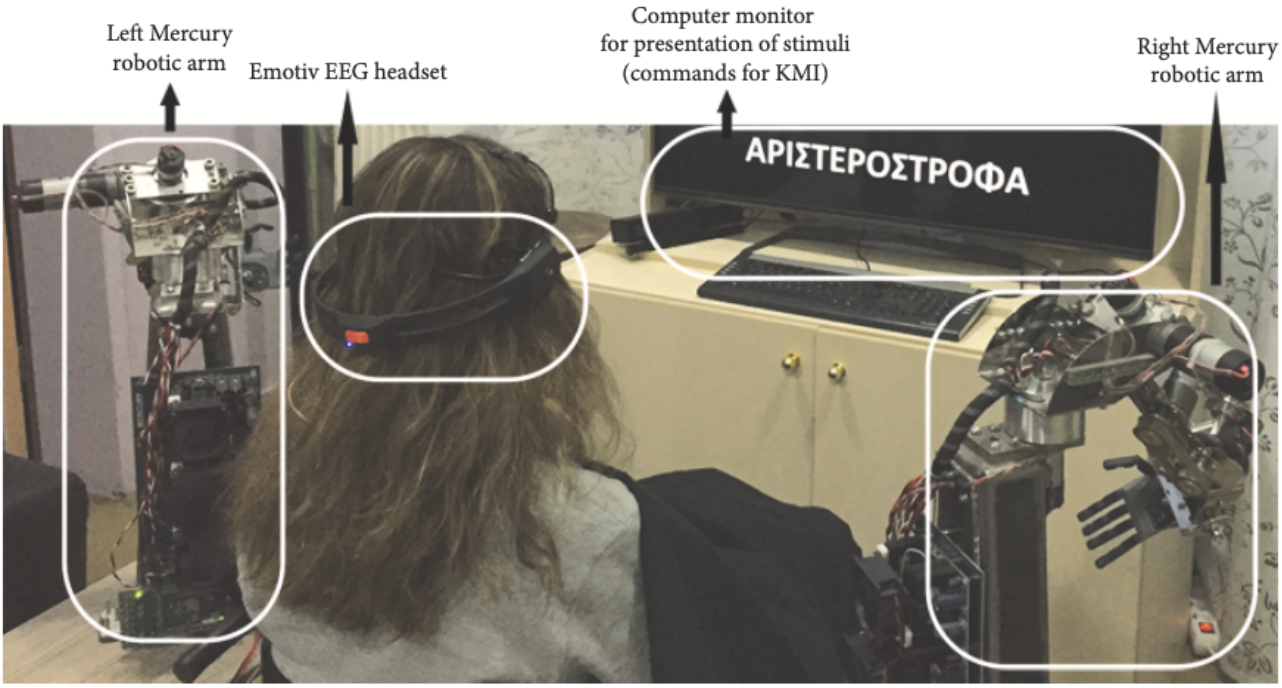
Figure 1. VMI under high-resolution EEG recording during presentation of multiple movements of the upper limb by patients with spinal cord injury in previous pilot experiment [3,16]. Figure from [16]. EEG: electroencephalography; VMI: visual motor imagery.



Mountable Robotic Arms Controlled With a Wireless Brain-Computer Interface

Participants during the 3 main sessions (initial, intermediate, and final) will train in kinesthetic motor imagery (KMI) to control the anthropomorphic 8-degree-of-freedom robotic arms (Mercury 2.0) that have been developed by the Lab of Medical Physics & Digital Innovation. Control will be achieved by a commercial-level, wearable, wireless 14-channel EEG-based BCI (the Emotiv EPOC). This experimental setup has already been tested by the authors with patients with SCI [16,17], achieving high rates of BCI performance and high degree of user acceptance of the robotic system (Figure 2).

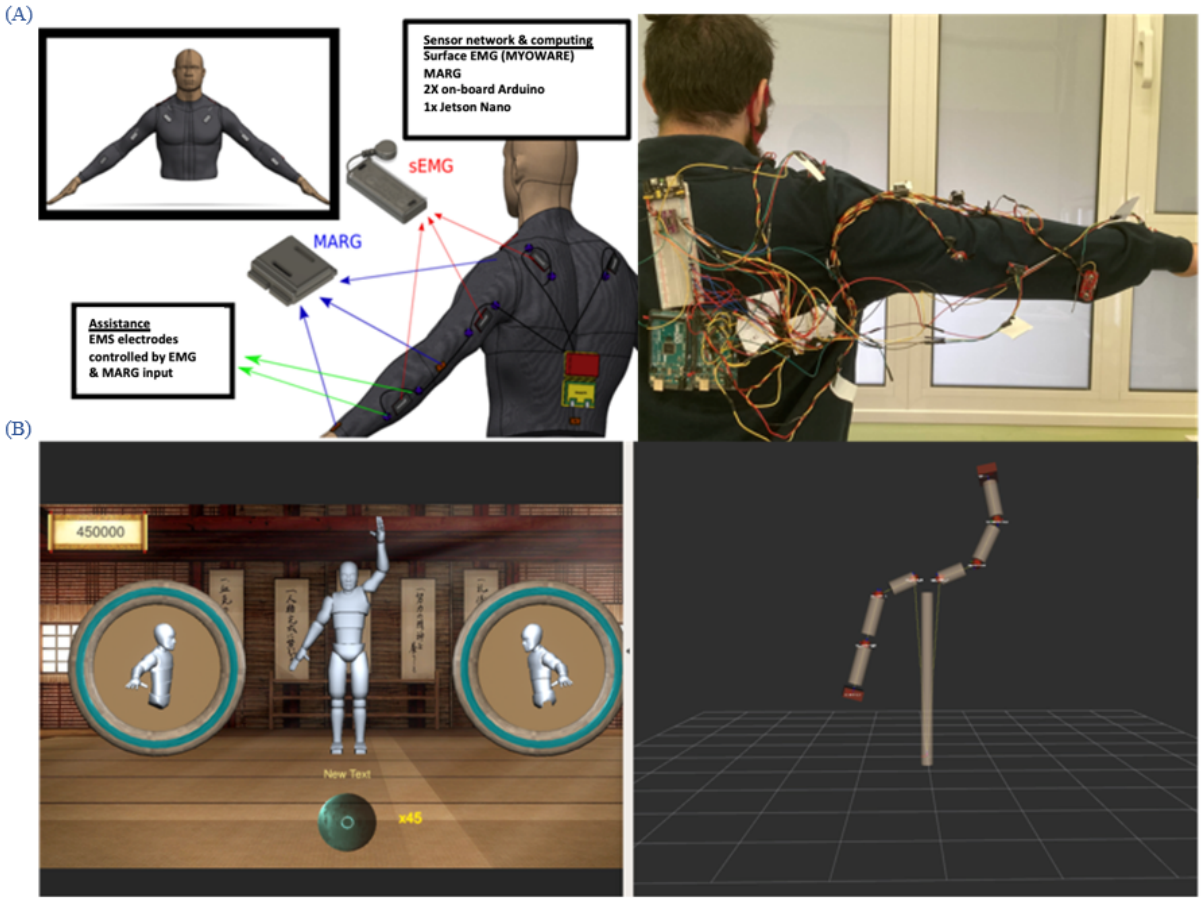
Figure 2. Pilot use of 8-degrees-of-freedom robotic arms by a 30-year-old patient with spinal cord injury with C6 tetraparesis, controlled by a commercial EEG-based brain-computer interface (Emotiv) through KMI [16,17]. Figure from [16]. EEG: electroencephalography; KMI: kinesthetic motor imagery.



A Body-Machine Interface Consisting of Wearable Robotics Jacket and Gloves in Combination With Serious Games Application

Our wearable device (wearable robotics jacket and gloves) was designed with the purpose of providing a real-time quantifiable evaluation of the wearers upper body kinematics and the accompanying biomechanical systems that enable them [15]. The device consists of 2 types of commercially available sensors, attached on the cloth of the wearable. Six 9-degrees-of-freedom magnetic acceleration rotation gravity sensors were placed on the links of 3D representation of the upper body kinematic chain. They are complemented by 14 surface electromyography (sEMG) sensors placed on the major muscle groups impacting the state of the joints in the aforementioned kinematic chain [18,19]. The information from the sensors is collected and transferred from an Arduino board to an Ubuntu-based computer, running a robot operating system environment. The data are then collected, with the information gathered by the inertial measurement units being used to calculate the angles of the joints where the connected links are attached. The calculated kinematic representation is then directed to a live visualization SG, created in Unity engine (Figure 3). Utilizing the live representation of the wearer's kinematics, in combination with EMG activity from the muscles that directly impact the kinematic chain, the user can train on prescribed tasks in the SG, while receiving assistance in the form of surface electrical muscle stimulation (EMS) according to desirable difficulty level.

Figure 3. (A) Schematic of sensors layer and photo of the wearable prototype. (B) Unity game snapshot and corresponding pose in the robot operating system (ROS) rviz tool. Figure modified from [18]. EMG: electromyography; EMS: electrical muscle stimulation; sEMG: surface electromyography.



Augmented Reality Module

This modality will use the Microsoft HoloLens 2.0 AR Headset and the Unity engine to project the NeuroSuitUp dojo-themed SG, as well as virtual robotic arms, and to provide the participants with an easy-to-use, readily accessible platform to train in task-specific movement of the arms (grasping, reaching) and different degrees of freedom while in an immersive AR platform [20]. Control will be provided by both EEG-BCI [21] and the BMI developed to train in an AR environment. The virtual avatar and arms will be fully anthropomorphic and motion will be fluid. The set up will also deploy an array of wearable sensors for physiological recording (heart rate, pressure, skin conductance) to assess affective parameters of neurorehabilitation.

Ethics Approval

The study was approved by the Committee for Bioethics and Ethics of the School of Medicine, Aristotle University of Thessaloniki with the protocol number 188117/2022 in the Committee sitting 68/13-7-2022 following the application with the protocol number 165080/2022.

Patient Population and Eligibility Criteria

Participants considered for recruitment are reviewed for the following eligibility criteria (inclusion and exclusion) by a member of the research team before enrollment.

Inclusion Criteria

The following criteria should be met by eligible participants before inclusion into the study:

- Participants (patients with SCI or healthy individuals) should be at least 14 years of age.
- Participants of the SCI group (complete or incomplete) should have a clinical diagnosis of SCI evaluated by the ASIA (American Spinal Injury Association) Impairment Scale (AIS).
- Participants of the SCI groups (complete or incomplete) should have sufficient documentation of the injury in neurological examination and a magnetic resonance imaging (MRI) scan of the injury level, as well as optional additional computed tomography or x-rays.
- Participants should be willing to follow the study protocol and procedures.
- Parents or legal guardian should voluntarily provide written consent for their child's participation in the study, in case participants are under 18 years of age.

Exclusion Criteria

The following criteria will result in the exclusion of participants from the study:

- Any other neurological condition that has a possibility to significantly impact the neurological status of the participants or the ability to control a BCI or the neurophysiological recordings:

  - traumatic brain injury
  - CNS tumors
  - multiple sclerosis
  - amyotrophic lateral sclerosis
  - Parkinson disease
  - refractory epilepsy
- Participation during the last 3 months in another interventional study, the effects of which could impact this study's observations.
- Other grave medical condition that could impact the participation or the safety of the participants:
  - cardiac deficiency
  - pulmonary deficiency
  - hearing and visual impairments that can impact the participant's understanding of the intervention and performance
  - illegal drug use
  - chronic alcoholism
- Parents who are not willing to provide written consent for their child's participation in the study.

A "Participant Information and Consent Form" is used to comprehensively inform all participants regarding the procedures of the study, the purpose of the study, and potential risks and benefits. The approval of the Ethics Committee with the protocol number is mentioned in the informed consent document. The informed consent documents use a unique user identification code for anonymization of personal information and will be signed by both the participants and the researcher that conducts the interview and information session as well as by the principal investigator of the study. A special section of the informed consent form for participants aged under 18 years requires the approval of their participation by their parent/guardian, without which they cannot take part in the study. Information provided in the consent form is described below:

- Participation is strictly voluntary.
- Participants have the right to ask questions about the study procedures before taking part in the study.
- All underlying risks or burdens of their participation would be made clear to participants beforehand.
- Participants will be made aware about what the benefits (scientific, otherwise) will be from this study.
- Participants will be informed specifically about how their data will be collected, handled, and protected during the project's lifetime as well as whether data will be destroyed or reused (in case there is a possibility to reuse them).
- Participants will have to agree with the further use of their data.
- Participants are informed that they can leave the study at any time or withdraw their data from the study.
- Participants will be informed about the possible commercial exploitation of the research.

Recruitment of Participants

Estimated enrollment to the NeuroSuitUp pilot study was set for 20 participants (10 patients with SCI and 10 age- and sex-matched healthy participants). The allocation is nonrandomized, nonblind with a parallel assignment intervention model controlled by a cohort of healthy participants and no masking (open label). There are 3 study arms: (1) experimental—complete injury at cervical spine (n=5 participants); (2) experimental—incomplete injury at cervical spine (n=5 participants); and (3) active comparator (n=10 healthy participants).

While the sample size in pilot trials is suggested to not fall within the requirements for power analysis [22], the enrollment for the NeuroSuitUp pilot study was estimated by having in mind the research experience of the research group with patients with SCI and their particularities from previous research projects [23] as well as suggestions from the literature [24,25]. The clinical trial is set to begin in August 2022, while patient enrollment into the clinical trial is estimated to begin in January 2023 and end by December 2023.

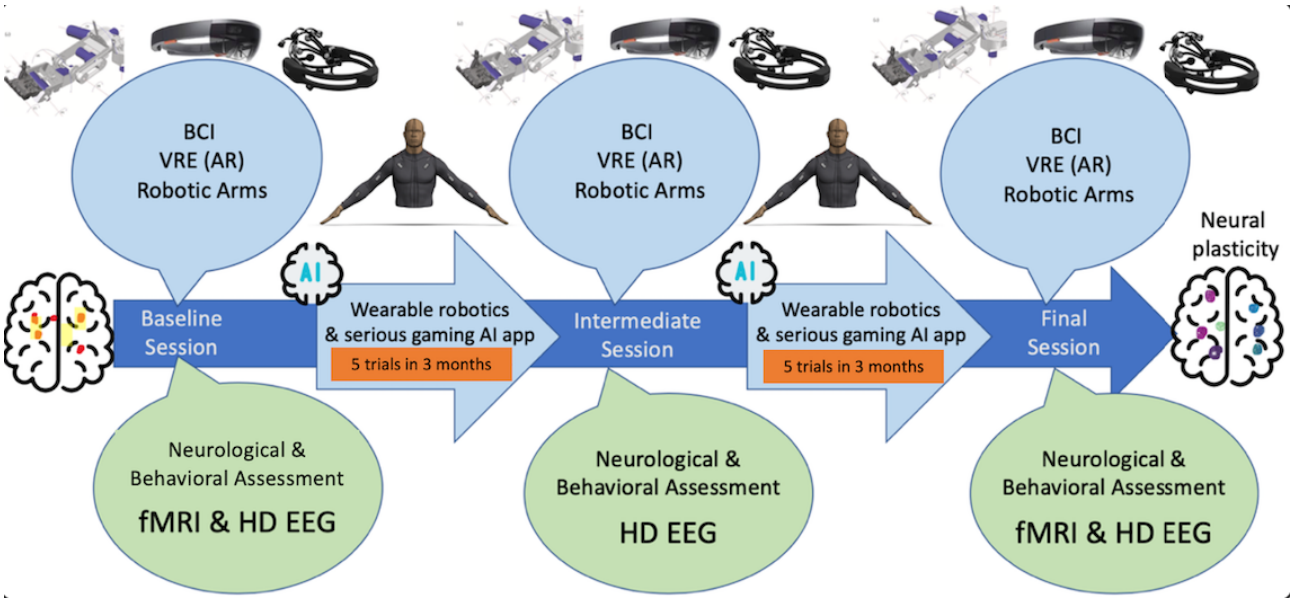
The participants will be selected from the SCI and healthy general population in Greece. As described before, the study design allows recruitment of patients at least 14 years of age. The inclusion of the adolescent population in the study was deemed necessary due to the bimodal distribution of SCI demographics [26,27], in which a large portion of the patients' age at the time of injury ranges from 13-16 to 30 years. SCI is very rare in ages lower than that due to reasons related to both skeletal immaturity and behavioral characteristics of preadolescent children. Recruitment will be facilitated by the Second Neurosurgical Department of Ippokrateio General Hospital of Thessaloniki and the Department of Physiotherapy of International Hellenic University that both support the implementation of pilot trials and the relevant dissemination activities. As such, patients with SCI can be reached through the patients previously or currently treated by these 2 departments and new patients can be prospectively informed about future possibilities in case their condition reaches the chronic phase. Moreover, the collaborating departments will assist in the dissemination of information to the relevant population and the public through their websites and patient organizations, through supporting dissemination events (information days, layouts) and through their participation in scientific publications.

Experimental Procedures

Overview

The intervention phase will be based on 3 main assessment sessions (initial, intermediate, and final), in which neurological, behavioral, and neurophysiological assessment (EEG) will be performed. Before the initial session, a brain MRI scan of the participants will also be performed. The 3 sessions will span across 6 months for each participant, 3 months between initial and intermediate, and 3 months between intermediate and final. The intervention procedures will consist of the 4 components described earlier. Between the main sessions, the participants will participate in regular training sessions of the BMI (wearable robotics) modality (5 sessions/3 months). The interventions are depicted in Figure 4.

Figure 4. Overview of the experimental procedures, based around 3 phases (initial, intermediate, and final assessments). AI: artificial intelligence; AR: augmented reality; BCI: brain-computer interface; fMRI: functional magnetic resonance imaging; HD EEG: high-density electroencephalography; VRE: virtual reality environment.



Initial Assessment Session

After signing the informed consent form, participants will be screened for inclusion and exclusion criteria and they will be administered the questionnaires presented in the relevant subsection. The participants (and together with their caregivers) will then be taken to the collaborating hospital for a functional MRI of the brain and will return to the Medical Physics and Digital Innovation Laboratory site. Breaks will be provided whenever requested by the participant. On-site, the participants will enter the EEG room to practice the VMI module and will then enter the Thess-AHALL Living Lab [28] room and practice controlling the robotic anthropomorphic limbs as described before. Finally, participants will additionally wear the Microsoft HoloLens 2.0 device and practice controlling an avatar and virtual limbs in an AR environment in multiple movements (multiple degrees of freedom) and functional object movement exercises, with control through mental movement and BCI. A range of wearable sensors for physiological recordings (heart rate, pressure, skin conductance) will also be included.

Intermediate and Final Assessment Sessions

The procedures of the intermediate and final assessment sessions are identical to the initial one with the exception of (1) signing an informed consent form, (2) screening for inclusion criteria, and (3) performing a functional brain MRI, all of which will not be repeated.

Regular Training Sessions

Participants will enter the Thess-AHALL Living Lab room and practice controlling a wireless wearable BMI (wearable robotics jacket and gloves) with limb position and pressure sensors, EMG, and EMS actuators with haptic feedback that will be used to train residual movements of the upper extremities. They will be asked to complete motor exercises within the dojo-themed SG. The exercises will include finger and hand movements and the reward method will include music and visual stimuli in different difficulty settings. Music in this setting will be used as both a control and a reward. A range of wearable sensors for physiological recordings (heart rate, pressure, skin conductance) will also be included. Breaks will be provided whenever requested by the participant. Finally, the participants will be given the test questionnaires presented in the next subsection.

Questionnaires

Initial, Intermediate, and Final Assessment Sessions

- International Standards for Neurological Classification of Spinal Cord Injury [1]
- AIS [1]
- Greek translation of the Spinal Cord Independence Measure, version III (g-SCIM-III) [29,30]
- Modified Ashworth Scale [31]
- Beck Depression Inventory (BDI) [32,33]
- Beck Anxiety Inventory (BAI) [34]
- Apathy Evaluation Scale—Clinician version (AES-C) [35]
- Rosenberg Self-Esteem Scale (RSES) [36,37]
- 10-item Kinesthetic and Visual Imagery Questionnaire (KVIQ-10) [38]
- Vividness of Visual Imagery Questionnaire (VVIQ) [39]
- GODSPEED Robotics Questionnaire [40]
- Subjective Mental Effort Questionnaire (SMEQ) [41]
- Locally Experienced Discomfort Questionnaire (LED) [42]

Regular Training Sessions

- GODSPEED Robotics Questionnaire [43]
- KVIQ-10
- SMEQ
- LED
- AES-C

Outcome Measures of the Pilot Study

Primary Outcome Measures

The BCI Control (Yes/No)

This is defined as the ability of participants to modulate brainwave activity to achieve control of the BCI. BCI control is evaluated as achieved or not (there are cases of BCI illiteracy when the participants cannot modulate their brainwaves to control the BCI). Time frame: after the initial assessment session.

The SG Performance (In-Game Scoring System)

This is defined as the ability of participants to control the wearable robotic jacket to complete in-game tasks and collect more points. The points will be gathered by matching the speed and position of the in-game task instructions while receiving assistance from EMS. Time frame: at the intermediate assessment session.

Secondary Outcome Measures

Initial Functional Improvement

This is defined as daily functionality as measured by the g-SCIM-III. Time frame: at the intermediate assessment session.

Intermediate Functional Improvement

This is defined as daily functionality as measured by the g-SCIM-III. Time frame: at the final assessment session.

Long-Term Functional Improvement

This is defined as daily functionality as measured by the g-SCIM-III. Time frame: 6 months after the final assessment session.

BCI Performance

This pertains to the classification accuracy (percentage of voluntary nonerroneous commands to overall number of detected commands) and bit rate (number of commands per minute): defined as the achieved performance on BCI at the conclusion of BCI sessions for each participant. Measured by classification accuracy (percentage of voluntary non-erroneous commands to overall number of detected commands) and by bit rate (number of commands per minute). Time frame: at the final assessment session.

Pilot Testing During Development

Before conducting the pilot study with formally enrolled participants in the protocols, we conducted test trials by healthy individuals, who tested the various components for feasibility of the protocol and especially the BMI consisting of wearable robotics jacket and gloves in combination with the SG application component. The BMI component as the most newly developed modality of the designed interventions and procedures was evaluated for easiness of use, for possible discomfort, and for the perception of the robotics game platform by the participants. They performed basic tasks (raising arms consecutively) attempting to match the arm position of the game avatar for 3 minutes. User experience was assessed by the SMEQ [6] and the LED [7] scales. Perception of the robotics game platform was assessed using the Greek version of the Godspeed Robotics Questionnaire (Godspeed-g-1.2). Participants also provided qualitative data in an open format.

Statistical Analysis

Statistical analysis of the preliminary data as well as of the final pilot study data will be performed using SPSS (version 26.0; IBM, Inc.) and the statistical significance level will be set at .05. Continuous variables are explored for normality by means of the Shapiro-Wilk test and the appropriate descriptive statistics (parametric/non-parametric) will be used accordingly. Normally distributed continuous variables are reported as mean (SD), while nonnormally distributed variables are reported as median and interquartile range (Q1-Q3). Regarding the test trials, possible associations between variables were investigated using the Spearman correlation coefficient.

Data Availability

Data from the NeuroSuitUp study will be made publicly available after the project's completion and will be accessible through the institutional project web page under an Attribution-NonCommercial-NoDerivatives 4.0 International license. Data of the preliminary analysis presented in this manuscript can be made available via a request to the authors following a Memorandum of Understanding in the context of Open Research Initiative.

Results

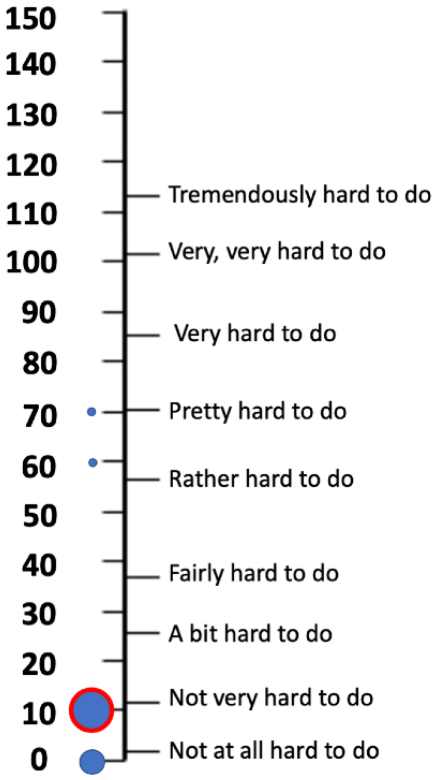
Demographics

In total, 10 participants (8 male and 2 female) with a mean age of 31.90 (SD 5.80) years participated in the test trials (conducted during March-May 2022) of the platform consisting of the wearable robotics and the SG application. Analysis of results from the main clinical trial will begin as recruitment progresses and according to completion of the 3 phases by the participant in a rolling fashion. Findings from the complete analysis of results are expected in early 2024.

Subjective Mental Effort Questionnaire

The participants in the test trials reported that the wearable robotics and SG platform were not very hard to use, as in the SMEQ scale the median rating was 10 (IQ1=5, IQ3=10) (not very hard to do). Most participants (8/10) answered either "not very hard to do" or "not at all hard to do," while only 2 participants answered either "rather hard to do" or "pretty hard to do," as seen in Figure 5.

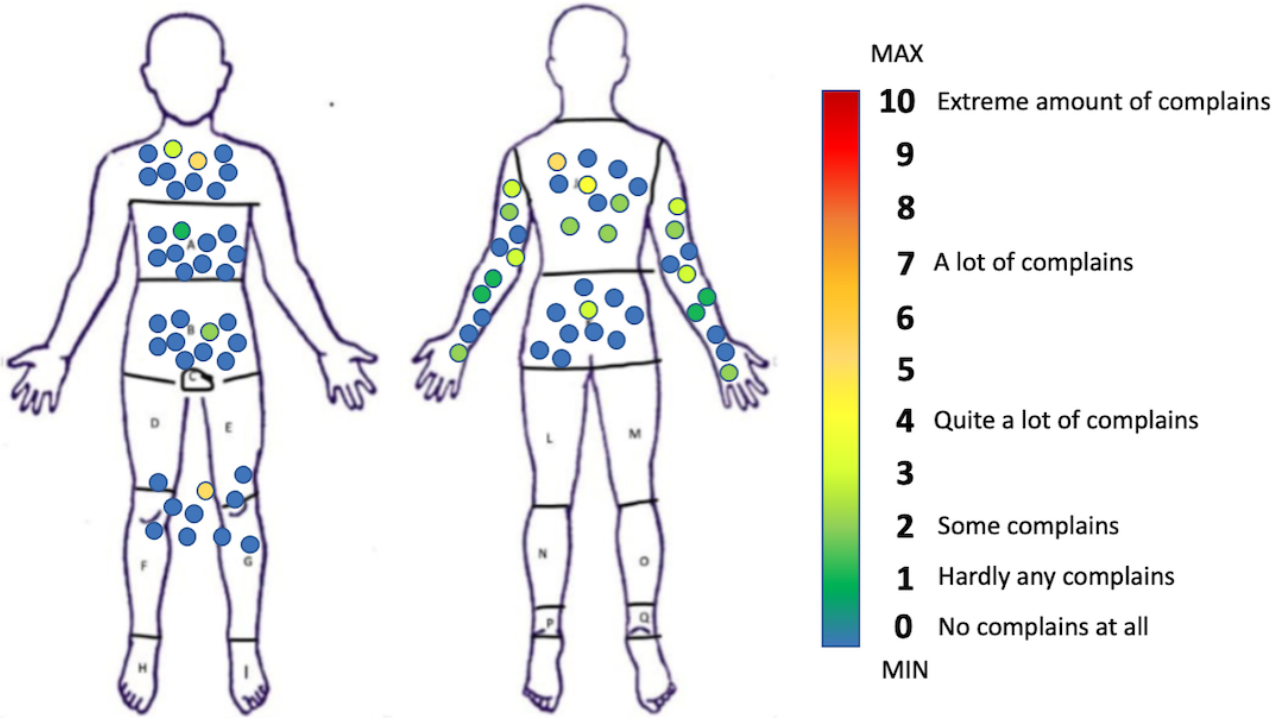
Figure 5. Answers of test trials participants to SMEQ. Size of the circles denotes relative number of answers. Red circle denotes median marking. SMEQ: Subjective Mental Effort Questionnaire.



Locally Experienced Discomfort

Very little local discomfort was elicited, as no body area was reported with a median over 1 in the LED scale and no participant utilized a marking of more than 5 in the same scale for any of the body areas. Most complains were reported in the back and the arms, as seen in Figure 6, which depicts all the answers of the participants for the different body parts. Both legs were marked as a single area, and so were the front and back surface of either arm.

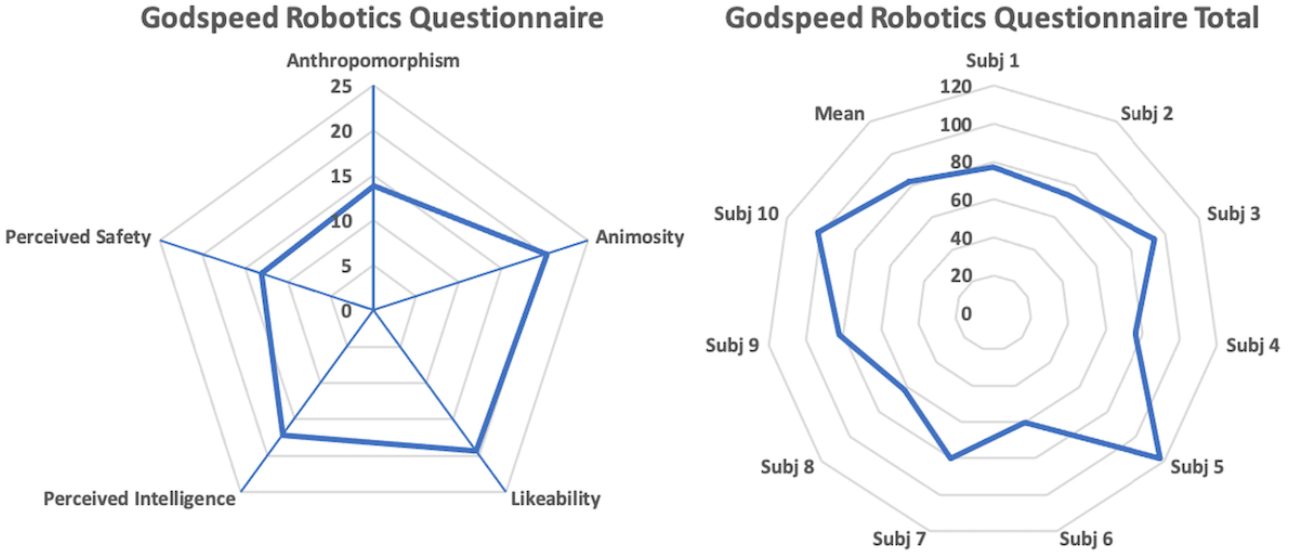
Figure 6. All answers of test trials participants to the Locally Experienced Discomfort Questionnaire according to body area. Color inside the circles corresponds to complain intensity according to colormap.



Godspeed Robotics Questionnaire (Godspeed-g-1.2)

The participants in the test trials perceived the robotics game platform positively, as mean total Godspeed score was 82.4 (SD 17.58; maximum 120). Regarding Godspeed subcategories, mean Anthropomorphism was 13.8 (SD 5.05; maximum 25), mean Animosity 20.2 (SD 5.51; maximum 30), mean Likeability 19.3 (SD 4.67; maximum 25), mean Perceived Intelligence 17.1 (SD 5.63; maximum 25), and mean Perceived Safety 13.1 (SD 2.80; maximum 20), as depicted in Figure 7. No correlations were revealed between questionnaires.

Figure 7. (A) Mean Godspeed robotics questionnaire scores by category. (B) Total Godspeed scores of all participants in the test trials.



Discussion

Expected Findings

In summary, according to the preliminary results reported before, the current test version of the platform was assessed as easy to use, causing little to no discomfort and generally viewed as a safe and positive experience by the participants at the test trials. This allowed the research team to proceed with the recruitment for the NeuroSuitUp pilot study, which, as described in the study design, will be a nonrandomized controlled clinical trial, assessing the use of the man-machine interfaces included in the platform by patients with SCI.

Regarding the arm including patients with incomplete injury, we hypothesized mild improvement in functional independence, as spinal cord independence measured is anticipated within main outcomes of the study. This would not only demonstrate the feasibility of the different noninvasive man-machine–based components of the platform as suitable treatment modalities for incomplete SCI at the cervical spine, but also validate previously reported results by patients with lower SCI, where those with dormant neural plasticity can be recruitable even in chronic SCI stages [6]. Such findings, if confirmed, could merit popularization of man-machine–based interventions for the majority of current incomplete SCI population.

Regarding the arm including patients with complete injury, functional improvement, while hypothesized, might not be observed due to the brevity and low intensity of the intervention. Nonetheless, the main outcomes for this arm (as well as the others) are BCI control and performance in the SG-wearable robotics module. Participation may prime such patients to the use of noninvasive interfaces, improve their perception of robotics [3], while also maintaining their motivation and improving their KMI capacity. Improvement in the main and secondary outcomes of the pilot study in this arm may prepare these patients for long-term commitment to relevant interventions. Finally, neurophysiological measurements (EEG, EMG, inertial motion units, and others) from the 3 phases and the training sessions of the study are anticipated to allow us to describe a model of CNS muscle activations and connectivity along injury severity and to further investigate adaptive and maladaptive neural plasticity phenomena.

Strengths and Limitations of the Study

The advantages provided by the NeuroSuitUp components are the multiple man-machine interfaces that are targeting both CNS and muscle system, the immersiveness of wearables and AR platform, the gamification motivation factor of the SG, and the synergistic nature of the different modalities. Components of the VMI and robotics arms have been previously tested in research projects and proven to be robust and feasible for such a scale of study. The advantages of the wearable components are the multitude of available measurements in real time, as well as the direct control of the intended movement through the intention-EMG-EMS-actuation bridge mediated by the SG training game. In short, the NeuroSuitUp platform offers a noninvasive and holistic solution for interventions in motor disability, such as in chronic SCI, as well as a multibiosignal recording platform to further understand and promote neurophysiological research in such conditions. Furthermore, through the use of the neuropsychological/behavioral battery, our study may enable quantitative data analysis assessing both behavioral characteristics and in-SG performance of the user.

However, there are also limitations that follow the use of noninvasive neural interfacing techniques both in recording, such as EEG and surface EMG (sEMG), and in actuation using EMS. sEMG infers an approximation of activations of

underlying muscle groups and may have limited sensitivity in alterations of impacted muscles activation. Similarly, few-channel EEG systems may be appropriate for use in BCI systems but their ability to decode complex motor intention or classify multiple mental commands is also limited. In this case, researchers are trading-off between noninvasiveness and unobtrusiveness from one side and quality and specificity of biosignals from the other, with the optimal choice being subjective to the application and implementation of the techniques. Regarding EMS, the prolonged use of neuromuscular stimulation may produce discomfort and fatigue effects that we are attempting to regulate through duty-cycle stimulation control and through optimization of the motor tasks regarded for training. Regarding the intervention protocol, the total (n=13) number of total sessions (10 assessment and 3 training) may impact adherence and lead to some participants dropping out, especially if no visible neurological improvement is noticeable. We plan to combat this risk by producing an entertaining SG module with many gamification elements to attempt to improve adherence to the protocol.

Future Work

Initial testing for the NeuroSuitUp wearable components, with 10 participants, provided necessary insight for further improvements, further enabling ease of use, comfort, and functionality. The efforts for the second version of the modality include on-board sensor stabilization for increased freedom of movement, software optimization to decrease any dissociation caused by a delayed response of the system, and modularization to further accommodate possible restriction of the wearer (ie, in wheelchair). We aim to enhance the platform by introducing several device improvements, including full power autonomy to improve unobtrusiveness as well as the design and development of assorted wearable robotics trousers, that will initially aim to gather EMG and magnetic acceleration rotation gravity information, while partially assisting with EMS; body weight support and rigidity will be examined in the future. In that direction, the inclusion of a BCI, in conjunction with the implementation of a hard exoskeleton through the use of lightweight, 3D-printed structures, will allow for the use of more advanced interfacing and control schemes. In particular, the combination of motor imagery potentials from a portable BCI and the preexisting inertial sensors would open the platform to patients that have no residual muscle activation, while the introduction of external pneumatic actuators on the exoskeleton would allow the system to circumvent physiological restrictions of the existing system, specifically muscle fatigue from the continuous use of the EMS. Finally, we aim to broaden the applicability of the platform in the coming months, with a version of the wearable system aiming at patients with stroke-related movement disabilities.

Conclusions

Chronic SCI is characterized by an often irreversible disability impacting functional independence. Wearable and soft robotics using body-machine and brain-machine interfaces for their control have been increasingly popular in neurological condition rehabilitation research. Immersive serious gaming applications have demonstrated added value in the ability to induce motivation and adherence to rehabilitation regimens. In order for such applications to achieve ethical and end user acceptance for everyday tasks, the use of noninvasive, unobtrusive, safe, and relatively low-cost systems is required. NeuroSuitUp could provide a valuable complementary platform for training in immersive rehabilitation methods to promote dormant neural plasticity. While motor control and assistance are the main focus of the platform, the used biosignals are able to track affect states of users in real time, assessing emotional impact [44], learning gain [45], as well as engagement and motivation to provide rehabilitation experience tailored real-time to user's interest, attention, and effort.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
External peer-review from the European Social Fund - Operational Programme Human Resources Development, Education, and Lifelong Learning 2014-2022 (Greece and European Union).
[PDF File (Adobe PDF File), 4903 KB - resprot_v11i9e41152_app1.pdf]

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Abbreviations

AES-C: Apathy Evaluation Scale—Clinician version
AIS: ASIA Impairment Scale
AR: augmented reality
ASIA: American Spinal Injury Association
BAI: Beck Anxiety Inventory
BCI: brain-computer interface
BDI: Beck Depression Inventory
BMI: body-machine interface
CNS: central nervous system
EEG: electroencephalography
EMG: electromyography
EMS: electrical muscle stimulation
fMRI: functional magnetic resonance imaging
g-SCIM-III: Greek translation of the Spinal Cord Independence Measure, version III
KMI: kinesthetic motor imagery
KVIQ-10: 10-item Kinesthetic and Visual Imagery Questionnaire
LED: Locally Experienced Discomfort Questionnaire (scale)
MRI: magnetic resonance imaging
ROS: robot operating system
RSES: Rosenberg Self-Esteem Scale
SCI: spinal cord injury
sEMG: surface electromyography
SMEQ: Subjective Mental Effort Questionnaire
US NIH/NINDS: US National Institute of Neurological Disorders and Stroke
VMI: visual motor imagery
VRE: virtual reality environment
VVIQ: Vividness of Visual Imagery Questionnaire

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Proposal

The Impact of a Digital Artificial Intelligence System on the Monitoring and Self-management of Nonmotor Symptoms in People With Parkinson Disease: Proposal for a Phase 1 Implementation Study

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Abstract

Background: Nonmotor symptoms of Parkinson disease are a major factor of disease burden but are often underreported in clinical appointments. A digital tool has been developed to support the monitoring and management of nonmotor symptoms.

Objective: The aim of this study is to establish evidence of the impact of the system on patient confidence, knowledge, and skills for self-management of nonmotor symptoms, symptom burden, and quality of life of people with Parkinson and their care partners. It will also evaluate the usability, acceptability, and potential for adoption of the system for people with Parkinson, care partners, and health care professionals.

Methods: A mixed methods implementation and feasibility study based on the nonadoption, abandonment, scale-up, spread, and sustainability framework will be conducted with 60 person with Parkinson–care partner dyads and their associated health care professionals. Participants will be recruited from outpatient clinics at the University Hospitals Plymouth NHS Trust Parkinson service. The primary outcome, patient activation, will be measured over the 12-month intervention period; secondary outcomes include the system's impact on health and well-being outcomes, safety, usability, acceptability, engagement, and costs. Semistructured interviews with a subset of participants will gather a more in-depth understanding of user perspectives and experiences with the system. Repeated measures analysis of variance will analyze change over time and thematic analysis will be conducted on qualitative data. The study was peer reviewed by the Parkinson's UK Non-Drug Approaches grant board and is pending ethical approval.

Results: The study won funding in August 2021; data collection is expected to begin in December 2022.

Conclusions: The study's success criteria will be affirming evidence regarding the system's feasibility, usability and acceptability, no serious safety risks identified, and an observed positive impact on patient activation. Results will be disseminated in academic peer-reviewed journals and in platforms and formats that are accessible to the general public, guided by patient and public collaborators.

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International Registered Report Identifier (IRRID): PRR1-10.2196/40317

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KEYWORDS

Parkinson disease; self-management; telemedicine; artificial intelligence

Introduction

Background

The aging population of the United Kingdom is expected to nearly double the prevalence of Parkinson disease by 2065 [1]. Parkinson disease significantly impacts patients, their care partners and families, and the health system of the United Kingdom. However, people with Parkinson disease are not monitored continuously or even frequently [2]; the National Institute for Health and Care Excellence guidelines currently recommend that people with Parkinson disease be reviewed every 6 to 12 months [3]. Nonmotor symptoms (NMS) of Parkinson can increase disease burden and decrease quality of life [4,5] but are often overlooked or undeclared in routine appointments [6]. Digital technology has the potential to improve the identification of NMS and enable more timely and appropriate treatment.

In this study, we will build on this evidence to implement improvements to a digital self-management system for nonmotor symptoms (NMS Assist) and to examine the impact of NMS Assist on patient activation and remote NMS monitoring (specifically the health care contacts triggered by that monitoring using NMS Assist). The high proportion of the UK population with internet access [7] means that this intervention could easily be made available on a large scale to people with Parkinson disease and their care partners.

Rationale

Benefits for People With Parkinson Disease and Care Partners

NMS Assist is expected to have several benefits for people with Parkinson disease and care partners; notably, by improving symptom monitoring by making assessments more timely, relevant, and convenient, by increasing disease and symptom awareness, and by supporting people with Parkinson disease and care partners in managing their NMS at home. A formative usability evaluation of 13 users (9 people with Parkinson disease, 4 care partners) demonstrated satisfaction with the system (System Usability Score 80%) [8].

The usability study identified 11 critical issues for improvement, centered on 3 themes: navigation, content, and accessibility [8]. These aspects of the system were subsequently refined based on participants' suggestions. To reduce the length of the NMSQ, people with Parkinson disease can complete partial assessments to monitor their symptoms. However, they are asked to complete the length of the Nonmotor Symptoms Questionnaire (NMSQ) every 6 months to ensure that a holistic assessment is performed, providing clinical safety netting.

Benefits for Health Care Professionals

NMS Assist will identify unmet need among people with Parkinson disease, and the adoption of a new system will add an element to the workload of health care professionals (HCPs); new skills will be needed to make clinical decisions based on the data developed. However, NMS Assist will provide HCPs with the ability to monitor and prioritize their patients efficiently. The main long-term benefit is the development of shared responsibility of health management with people with Parkinson disease, achieving the ambitions of the National Health Service (NHS) Long Term Plan with digitally enabled care and delivery of predictive, personalized, preventive and participatory care medicine, with improved support for care partners [9]. In time, this may result in fewer NMS-related complications (eg, falls), hospitalizations, and institutionalized care.

Benefits for Parkinson Disease Research

Ongoing collection of data will enable a longitudinal database. This will enable evaluations to identify clusters of NMS and associations between NMS and people with Parkinson disease and care partner characteristics. The value of this database for research would only be increased if NMS Assist was adapted and adopted in countries worldwide. For instance, it would enable examining global similarities or differences in symptoms and symptom clusters, quality of life impairment, and impact on care partners.

Theoretical Frameworks

The nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) framework [10] that aims to help predict and evaluate the impact of digitally enabled health programs was used to support the conception and development of the study plan. It was chosen as the main theoretical framework to ensure that the evaluation would examine a holistic set of variables essential to the long-term success and sustainability of the NMS Assist system. Qualitative data will be collected through semistructured interviews with a subset of users structured according to the theoretical framework of acceptability [11]. The use of both quantitative and qualitative methods to evaluate usability will enable the data to be triangulated.

These 2 frameworks will form the theoretical basis for the evaluation of NMS Assist:

- Long-term adoption and suitability to further trials will be evaluated using the NASSS framework [10]. This framework is important to include because interventions can only add value if they are successfully adopted and used. This framework emphasizes the consideration of the multiple levels—individuals and systems—that influence adoption and nonadoption.

- The theoretical framework of acceptability will be used to structure the semistructured interview guide [11]. This framework was chosen because it was developed specifically for health interventions, captures a multifaceted view of acceptability (with 7 components), and emphasizes the importance of considering different time points when evaluating acceptability [11].

Research Question

The main research question for the study is as follows: How does a digital remote monitoring and education system (NMS Assist) impact patient activation, symptoms, and quality of life for people with Parkinson disease and care partners?

Aims and Objectives

The study will assess the impact of NMS Assist on people with Parkinson disease, their care partners, and their Parkinson care team. Evidence regarding the system's perceived impact on knowledge, confidence, and skills at managing NMS and its safety, acceptability, and usability will improve the product design and determine readiness for advancement for wider adoption.

To achieve this aim, there are 5 key objectives:

- Assess the impact of the NMS Assist system on patient activation, symptom burden, and quality of life in people with Parkinson and their care partners
- Examine the impact of the NMS Assist system on contact between people with Parkinson disease and HCPs
- Assess the acceptability and usability of the system and identify any barriers to use for people with Parkinson, their care partners, and health care professionals
- Assess the cost impacts of the system compared to the standard of care
- Establish whether there is sufficient evidence of the impact of NMS Assist on the knowledge, confidence, and skills of people with Parkinson disease managing NMS, the identification of new or problematic NMS, and the prompting of health care contacts to justify more extensive trials

Based on evidence gathered from previous studies and our understanding of state of the art concerning digital health technologies and ongoing work with digital tools used with people with Parkinson disease, we hypothesize the following:

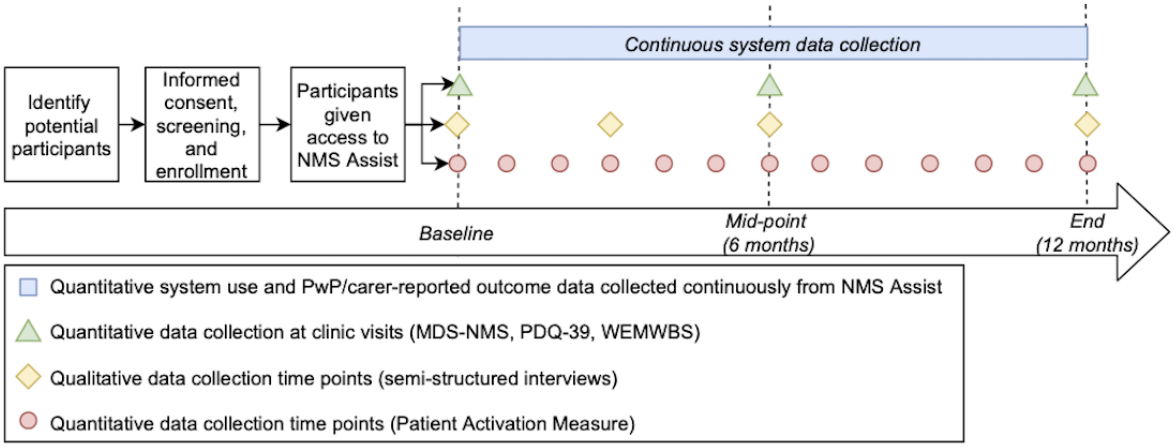
- NMS Assist will be acceptable, accessible, and engaging for users
- Use of NMS Assist will be feasible within an NHS service
- NMS resources will have a positive impact on patient activation (knowledge, skills, and confidence)

Methods

Study Design

This investigation will be a mixed methods feasibility study using an implementation science theoretical framework [12] to examine the research question. Quantitative methods will be used to evaluate NMS Assist's impact on patient activation as well as to examine health and well-being outcomes, usability, and engagement. Qualitative methods, specifically semistructured interviews, will also be used to gather a more in-depth understanding of the acceptability, usability, and engagement of users with NMS Assist (see Figure 1 for an overview). The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist was used to ensure the proposal was meeting content and quality standards (Multimedia Appendix 1) [13].

Figure 1. Study sequence diagram. NMS: Nonmotor symptoms. PwP: People with Parkinson disease. MDS-NMS: Movement Disorder Society–Nonmotor Rating Scale. PDQ-39: Parkinson's Disease Questionnaire–39. WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale.

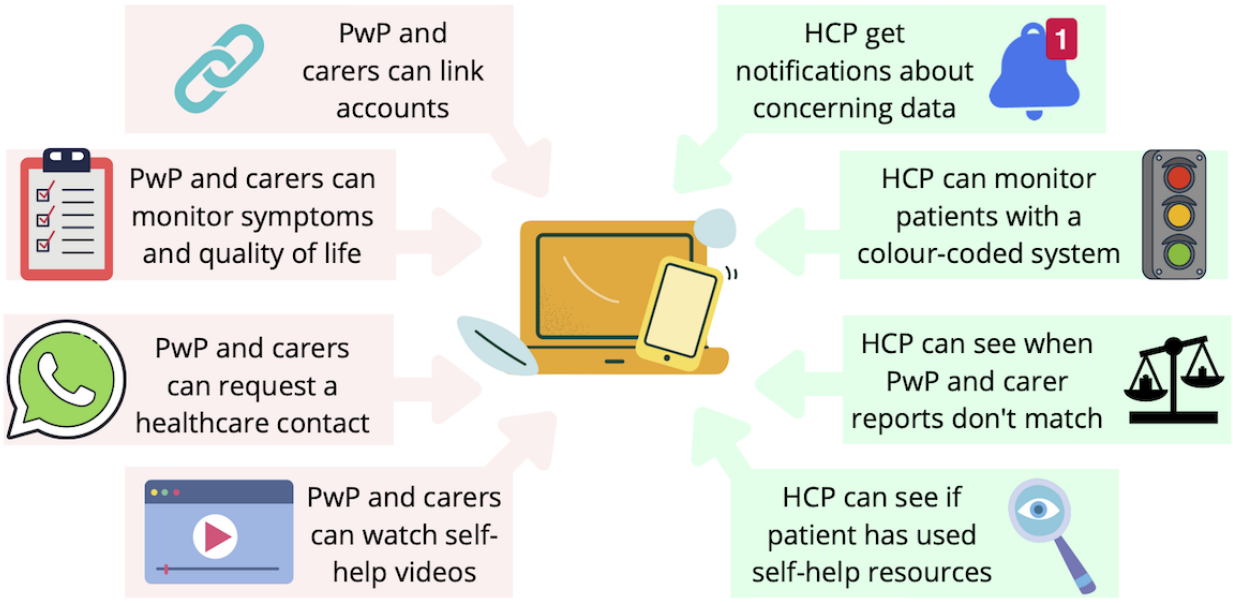


Intervention

NMS Assist is a patient engagement system that comprises a front-end patient engagement app and a back-end clinical data management system. Patient engagement systems can communicate with patients to collect data, provide feedback and educational resources, and support the management of a patient-provider relationship. For all Parkinson symptoms, there are pharmacological and nonpharmacological approaches to management. As motor symptoms are already well-supported by digital health solutions, NMS Assist focuses on the nonpharmacological approaches to nonmotor symptoms. It provides initial support for people with Parkinson disease and care partners to identify and manage their NMS before they can

be seen by an HCP or need medication. The system's self-help resources go through the first 3 steps that an HCP would explore with a patient: (1) identifying and describing the symptom using validated questionnaires (Nonmotor Symptoms Questionnaire [NMSQ] [14], Parkinson's Disease Questionnaire–8 [PDQ-8] [15], and Parkinson's Disease Questionnaire for Carers [PDQ-C] [16]), (2) explaining why it happens in Parkinson, and (3) providing nonpharmacological approaches to managing it. The system then has the ability to request health care contact for people with Parkinson disease who are still struggling to manage their symptoms so that the HCP can explore further measures. Steps 2 and 3 are supported by self-help videos that use diverse characters and were designed to ensure visual discrimination and easily translatable captions to address visual, hearing, and motor difficulties. The app is also designed to allow care partners to record and monitor their well-being and how they feel the person with Parkinson disease is getting on (see Figure 2). The intervention will be delivered in addition to usual care to the person with Parkinson disease.

Figure 2. NMS Assist system features. PwP: People with Parkinson disease. NMS: Nonmotor symptoms. HCP: health care professionals.



Sample Selection and Recruitment

People with Parkinson disease attending outpatient clinics through the University Hospitals Plymouth NHS Trust Parkinson service are eligible for this study (see Textbox 1 for eligibility criteria). All people with Parkinson disease and care partners who are willing and eligible will be included, with the intention of recruiting a representative sample based on various demographic and Parkinson-specific characteristics. The participants invited to the semistructured interview will be randomly selected from within different demographic and disease characteristic categories; we will continue recruitment in the semistructured interviews until we have reached demographic saturation to ensure we complete in-depth qualitative understanding of the impact of the system.

Recruitment will take place through the Plymouth Parkinson service. People with Parkinson disease attending outpatient clinics at the Plymouth Parkinson service will be invited to participate in the study along with their care partner. The associated HCPs responsible for the care of people with Parkinson disease and care partner dyads who consent into the study will then be invited to participate as well. Patients will be recruited during clinical appointments with the Plymouth Parkinson service by research nurses who will provide them with a paper participant information sheet to consider and will collect verbal or written consent using a preestablished informed consent form. Associated HCPs of the people with Parkinson disease who consent into the study will be invited to participate in the study for use of the clinician portal (and provided with an HCP version of the participant information sheet and informed consent form).

Textbox 1. Selection criteria. NMS: Nonmotor symptoms.

Inclusion criteria:

- Willing and able to provide informed consent and comply with intervention requirement
- Aged 18 years or older
- Be fluent in English
- Not resident in a care or nursing home
- Ambulatory
- Have compatible smartphone and data access
- Normally under the care of the Parkinson service in the participating organization
- Participant's health care professional in the participating organization consented to participate in the study

Exclusion criteria:

- Incapable of self-consent
- Secondary cause of parkinsonism
- Significant cognitive impairment or a diagnosis of Parkinson disease dementia
- Living in residential care facilities
- Previous involvement in development or testing of the NMS Assist system
- A life expectancy of <6 months
- Significant comorbidity, which in the opinion of the chief investigator would preclude safe participation in the study or protocol compliance
- In a dependent or unequal relationship with the research or care teams or any patient and public involvement representatives

Sample Size

We will recruit 60 people with Parkinson disease–care partner dyads and their associated HCPs—the exact number of HCPs cannot be determined until the people with Parkinson disease–care partner dyads have been recruited, as we will include HCPs who are associated with those patients. Of the 60 dyads, at least 20 people with Parkinson disease–care partner dyads will be purposively sampled for a semistructured interview. We will also be inviting the HCPs associated with those dyads to separate semistructured interviews.

Since this is a feasibility study, a formal sample size calculation has not been performed. A sample size of 60 people with Parkinson disease–care partner dyads was selected because this is an achievable number of patients to recruit within the study period based on our prior research.

Outcomes

Primary Outcome

The primary outcome, patient activation, will be assessed using the Patient Activation Measure [17]. The concept of patient activation refers to patients having the necessary knowledge, confidence, and skills to manage their own health and well-being. It is important to note that as this study design is centered on feasibility, the evidence captured will not measure efficacy. Should there be indications of a positive impact of the NMS Assist system on patient activation and health and well-being outcomes, efficacy will be tested in further studies.

Secondary Outcomes

There will be several secondary outcome measures to assess health and well-being outcomes, safety, feasibility, usability, and acceptability (see Textbox 2).

Textbox 2. Secondary outcomes and measures. EQ-5D-5L: EuroQol 5 Dimension 5 Level. NMS: Nonmotor symptoms.

1. Health outcomes
- Nonmotor Symptoms Questionnaire [14]
- Movement Disorder Society–Nonmotor Rating Scale [18]
- Parkinson's Disease Questionnaire–8 [15]
- Parkinson's Disease Questionnaire–39 [19]
- EQ-5D-5L [20]

2. Well-being outcomes
- Warwick-Edinburgh Mental Wellbeing Scale [21]
- Parkinson Disease Questionnaire for Carers [16]

3. Safety
- Aggregated evaluation results
- Adverse event reporting

4. Healthcare contacts
- Number of patient-initiated contacts with health care team (through the 'request health care contact' feature)
- Number of health care professional–initiated contacts (NMS Assist system has identified a need for clinical intervention based on patient- or care partner–reported data and prompted the health care professional to contact patient) recorded by the system

5. Feasibility
- Technical issues identified from the system use data
- Technical issues identified by participants

6. Usability
- System Usability Scale [22,23]
- Qualitative feedback from semistructured interviews

7. Acceptability
- Qualitative feedback from semistructured interviews (structured using the theoretical framework of acceptability) [11]

8. Engagement
- System use data (trend of use over time)
- Qualitative feedback from semistructured interviews

9. Costs
- Cost analysis will be used to examine the factors impacting costs for implementing the system

Health and Well-being Outcomes

A key element of the NMS Assist system is the use of validated questionnaires, and several of the health and well-being outcomes will be measured through the app—including the NMSQ [14], the short form of the PDQ-8 [15], and the PDQ-C [16]. The questionnaires have been validated in several different populations (eg, NMSQ [14,24-26], PDQ-8 [27-31]), suggesting that the measurement properties are appropriate for people with Parkinson disease in different contexts [32].

During the clinic visits (at baseline, 6 months, and 12 months), health and well-being outcomes will be assessed using the long-form PDQ-39 [19], the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [21], the Movement Disorder Society–Nonmotor Rating Scale (MDS-NMS) [18], and the EQ-5D-5L (EuroQol 5 Dimension 5 Level) [20]. These validated measures will be used to gather more in-depth data about people with Parkinson disease symptoms and their impact on people with Parkinson disease and care partner well-being to provide additional evidence of the impact of the system on health and well-being. This will also enable an assessment of the validity of home-collected measures.

Safety

We do not anticipate any significant safety risks from the intervention as the self-help guidance was collected from

credible resources, but safety will be assessed by maintaining an adverse event report log.

Health Care Contacts

The use of the health care contact function will be assessed by examining the number and frequency of people with Parkinson disease– and HCP-initiated contacts through the system.

Feasibility

Feasibility will be assessed by examining any technical issues identified in the system and system use data (including logs of complaints made by participants during the intervention delivery period) as well as asking participants about any technical issues they encountered when using NMS Assist during the semistructured interviews.

Usability

Usability will be assessed using questions presented to people with Parkinson disease, care partners, and HCPs delivered by online or paper surveys distributed to participants during their clinical visits at the beginning, midpoint, and end of the study delivery period. These questions will be drawn from the System Usability Scale [22]. Usability will also be assessed during the qualitative semistructured interviews by asking about any usability issues or barriers (not due to technical malfunctions) encountered by the users.

Acceptability

The acceptability of NMS Assist will be assessed during qualitative interviews with a subset of the people with Parkinson disease, care partners, and HCPs. These semistructured interviews will enable participants to provide more in-depth feedback about what they liked about NMS Assist and any barriers or frustrations they experienced using the system. The theoretical framework of acceptability will be used to structure the questions asked about acceptability in the semistructured interview guide because it considers several different facets of acceptability before, during, and after the intervention delivery [11]. Perceived acceptability at these different time points is likely to have an impact on the adoption and sustained engagement with NMS Assist.

Engagement

System use data will be collected to gather data about participants' engagement with the NMS Assist system. However, system use data only captures one component of engagement and is not a valid measure of engagement on its own [33,34]. Engagement has cognitive, behavioral, and affective aspects [34-37], and engagement with a digital health intervention includes engagement with the system itself, with various components of the intervention, and with the health behaviors it is trying to support. Therefore, system use data will be supplemented with semistructured interviews and a user engagement questionnaire (eg, the eHealth Engagement Scale [38] or the User Engagement Scale [39]) to gain a better understanding of user experience engaging with the intervention and the recommended behaviors.

Costs

A cost analysis impact of implementing the NMS Assist system will be conducted. Resource use (time spent on the system) and costs to implement throughout the 12-month intervention period to be compared to published data on costs for the standard of care.

Study Duration and Follow-up

The study will consist of 3 main phases over 24 months: preparation (6 months), delivery of the intervention (12 months, see Figure 1 for follow-up data collection points), and analysis and dissemination (6 months). The study team will monitor the use of NMS Assist and assure the system is being used within designed parameters during the study. No incentives will be provided to encourage adherence; the study is assessing the use of NMS Assist in the real world, and we expect that the benefits for people with Parkinson disease and care partners provided by the monitoring and self-help features will sufficiently encourage adherence to the study.

Data Collection

The evaluation shall follow the NASSS framework [10] that aims to help predict and evaluate the impact of digitally enabled health programs (see Table 1).

Table 1. Description of quantitative and qualitative data collection strategies structured using the nonadoption, abandonment and challenges to the scale-up, spread, and sustainability framework [10].

NASSS[a] domain and participants	Quantitative data	Qualitative data (topics in SSI[b])
Illness or condition		
All	Participant characteristics (eg, age, sex, cognitive impairment, depression, digital literacy)	Appropriateness of the system for individual context
People with Parkinson disease and care partners	Disease characteristics	—[c]
Technology		
All	Usability	Usability (barriers and facilitators to use)
All	—	Perceptions of system features, data privacy, and security
HCP[d]	System use data	Perceptions of the data provided by the system and use of data to improve understanding or inform care decisions
People with Parkinson disease and care partners	System use data	Perceptions of self-management resources and system feedback
Value proposition		
All	—	Motivation to participate in the study
All	—	Suggestions for system improvement
People with Parkinson disease and care partners	Care partner quality of life	Perceptions of impact of system on confidence, knowledge, and skills for managing nonmotor symptoms.
People with Parkinson disease and care partners	Nonmotor symptoms and their burden	Perceptions of impact of system on symptom burden
People with Parkinson disease and care partners	Patient functioning and well-being	Perceptions of impact of system on quality of life
People with Parkinson disease and care partners	Patient's knowledge, confidence, and skills (patient activation) at managing their health care	—
—	Costs and time commitments will be evaluated as part of the cost assessment using quality of life data collected in the study and published data on existing care treatment costs	—
Adopter system		
All	—	Acceptability
All	—	Barriers and facilitators to adoption
HCP	Characteristics of high and low system users	Reasons for high or low engagement with system
People with Parkinson disease and care partners	Proportion who completed questionnaires and frequency of completion	Effort required to learn and use the system
People with Parkinson disease and care partners	Proportion who accessed the self-help resources relevant to their specific symptoms (as reported on the NMSQ[e])	Perceived impact of system on care partner burden
Organization		
HCP	System use data (eg, number of log-ins per user, time spent on system, number of notifications responded to or actioned)	Issues reported with implementing the system in care practices
HCP	—	Perceptions of impact of system on routine care processes, workflows, and workloads
Wider context		
—	Implications for the national standards of care and inclusion in preexisting care pathways will be investigated	—

NASSS[a] domain and participants	Quantitative data	Qualitative data (topics in SSI[b])
Embedding and adaptation over time		
All	Participant retention throughout the study period	Reasons for continued/discontinued use of system during study
All	System use data (engagement) throughout study period	Perspectives on continued use and adaptations of the system in future
—	Costs and time commitments will be evaluated as part of the cost assessment using quality of life data collected in the study and published data on existing care treatment costs	—

[a]NASSS: nonadoption, abandonment and challenges to the scale-up, spread, and sustainability.

[b]SSI: semistructured interview.

[c]Not applicable.

[d]HCP: health care professional.

[e]NMSQ: Nonmotor Symptoms Questionnaire.

Quantitative Data Collection

The primary outcome, patient and care partner activation, will be completed at the beginning of the intervention period and monthly thereafter to measure the impact of NMS Assist on the knowledge, confidence, and skills of people with Parkinson disease and care partners over time [17] (see Figure 1). People with Parkinson disease and care partner scores on the NMSQ, PDQ-8, and PDQ-C will be recorded automatically by the system. The proportion of people with Parkinson disease who are contacted by their nurse or clinician based on their symptom questionnaire responses will be measured. Quantitative app and portal use data will be captured by the system to examine patterns of engagement with the questionnaires, self-help resources, and triggered health care contacts. Data about participant characteristics, recruitment, and retention will also be recorded.

Participants will also be asked to attend 3 study visits, at baseline, 6 months, and 12 months (see Figure 1), where they will complete the long-form PDQ-39 [19] and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [21] and will have administered the Movement Disorder Society–Nonmotor Rating Scale (MDS-NMS) [18] and the EQ-5D-5L [20].

Qualitative Data Collection

Qualitative data will be collected at 4 time points: baseline, 3, 6, and 12 months (see Figure 1). Purposive sampling will identify 20 participants, including people with Parkinson disease (with various demographic and disease characteristics), care partners, and HCPs, for qualitative semistructured interviews. The interviews will assess the system's acceptability structured using the theoretical framework of acceptability [11]. They will also explore participant motivation to participate, their engagement with the system, and any barriers or facilitators to use, usability issues, or technical difficulties they encounter. The perceived impact of the system on the knowledge, confidence, skills, and symptom burden of people with Parkinson disease and care partners will also be investigated to triangulate with the quantitative measures.

Data Analysis

The primary analysis will be the comparison of mean Patient Activation Measure scores [17] at each month. A repeated measures analysis of variance will be conducted to identify any significant changes in mean Patient Activation Measure scores over the 13 time points (baseline and monthly until 12-months postbaseline). If the normality assumption for a repeated measures analysis of variance is not met, a nonparametric alternative will be used.

The same analysis for the primary outcome will be conducted for the health and well-being outcome measures and the System Usability Scale, comparing the measure scores at the baseline, midpoint, and end points. Exploratory analyses will be conducted to identify potential associations between demographic or disease characteristics and outcome measures to inform hypotheses for future evaluations. All other quantitative data will be analyzed using descriptive statistics.

Semistructured interviews will be coded by 2 investigators using thematic analysis [40]. Triangulation of the quantitative questionnaire, system use, and qualitative semistructured interview data will be conducted to validate findings.

Ethical Considerations

Ethics Approval

Ethical approval is being sought from the Health Research Authority and the relevant Research Ethics Committee [41]. The study is registered at ClinicalTrials.gov [NCT05414071].

Confidentiality, Data Management, and Consent

The NMS Assist system will store identifiable data as part of the clinical record. The solution is in compliance with the UK Data Protection Act 2018 [42]. Each participant will be given a unique identifier with the key stored securely for reference purposes. Only the researchers will have access to research data and only the HCPs will have access to their patients' clinical data. Interview recordings will be anonymized and destroyed following transcription. After having the opportunity to review the participant information sheet, which explains the study procedures and provides clear information (reviewed by the people with Parkinson disease and care partner coapplicants)

about confidentiality, data privacy, and security and participant rights, participants will be asked to provide explicit consent for specific aspects of the study and data management.

Recruitment

Participant eligibility will be determined by the screening process they undergo in outpatient care at the University Hospitals Plymouth NHS Trust. All eligible participants will be invited to participate with no influence from the researchers. Interview participants will also be randomly selected (from demographic groups) by a computer script of intervention users. All participants will be included in the process evaluation's quantitative analyses, thus avoiding recruitment bias.

Power Relations and Other Potential Biases

Preestablished inclusion and exclusion criteria will be used to avoid any potential bias from the researchers as well as any coercion from participants. To prevent participation bias, only participants who would not otherwise progress down the standard care pathway will be excluded.

Sensitivity

The outcomes measures that concern potentially sensitive topics (personal health and well-being) will be delivered to the patients' phones via the app or by their HCP in a standard clinical setting. This enables them to avoid discussing any sensitive topics with a researcher. The semistructured interview questions will focus only on the participants' experiences with the app (engagement and acceptability) and are intended to avoid any areas of cultural or psychological sensitivity.

Timing

To mitigate any time concerns for participants, qualitative interviews will last for a maximum of 60 minutes. If this is a concern for any of the people with Parkinson disease, the interviews can take place over 2 sessions.

Study Governance

A project management group comprising the chief investigator, coinvestigators (including patient and public involvement [PPI] coinvestigators), an external researcher, and additional PPI representatives from the Community for Research Involvement and Support by People With Parkinson Diseases (King's College London) will review progress to provide study governance and oversight and to ensure there are no ethical concerns with the study. Planned deviations or waivers to the protocol are not allowed under the UK regulations on clinical trials and will not be used.

Safety Considerations

A comprehensive risk register and hazard log has been maintained for NMS Assist across its development as part of its clinical safety management file. This risk register will be regularly reviewed and updated as part of the project management governance. Key risks for this project include the following:

- Clinical: people with Parkinson disease, care partners, or HCPs are unwilling to incorporate the system into routine use; mitigated by a prior extensive cocreation process focused on user-centered design
- Excessive screen time: health risks associated with excessive screen time are mitigated encouraging users to complete the strategies and skills taught by the app away from the screen. All risks and mitigations are outlined in the clinical safety management file
- Technical: the system provides inappropriate decision support for clinicians; mitigated by supervision by the clinical research team, review of any errors, and extensive safety evaluation

Results

The study was awarded funding for 24 months in August 2021. Data collection is expected to begin in December 2022 and the study is expected to be completed by March 2024.

Discussion

Anticipated Findings

The evaluation is expected to show that the NMS Assist system has a positive impact on patient and care partner knowledge, skills, and confidence at managing NMS and general well-being. In addition, the results are expected to demonstrate the acceptability and accessibility of the system for users and its feasibility for implementation within NHS services.

Strengths and Limitations

A key strength of the intervention and study protocol is their co-design and development with PPI coinvestigators. The full execution of the study will be conducted in collaboration with PPI coinvestigators and other PPI representatives. Another strength is that the study has a long follow-up period (12 months) over which participants can use the NMS Assist system, which will enable an examination of the sustainability of the system's adoption in clinical and home settings.

A limitation of the study is its ability to assess the health and well-being outcomes measured. The study design does not enable a comparison between groups, which would provide stronger evidence of the system's potential impact. The generalizability of the results is also limited by the system, which requires that participants own a compatible device and be fluent in English.

Dissemination Plan

Analysis of the data will be compiled into a published peer-reviewed paper. People with Parkinson disease, care partners, and HCP investigators involved in the project will be integral in disseminating the results. PPI representatives will help develop and edit communications for all audiences, but, in particular, the summary of results that will be sent to all study participants. They will take the lead in disseminating and presenting results to the broader Parkinson community and professional groups such as through patient networks, the Parkinson's UK research network, patient and care partner congresses and conferences and the World Parkinson's Congress (which includes patients and professionals), newsletters, articles, and social media. Academic members of the project team will

disseminate the results through peer-reviewed journal publications and at research conferences.

The newest version of NMS Assist will be made publicly available to people with Parkinson disease and care partners after the system refinement stage (6 months after project commencement). This access will be available concurrent to our study, and members of the public will have the ability to consent into the study if they choose. We will make the data collected by NMS Assist freely accessible for research purposes by creating a data set that can be stored and shared securely in a data safe haven. To ensure that this data asset is used most appropriately, we will consult with Parkinson's UK and other stakeholders when developing our data sharing policy. In future, this will enable us to provide free and secure access to the data for people who apply to use it for research purposes, while accounting for data security and ethical considerations.

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Data Availability

Data will be available on request from the corresponding author but will not be publicly available due to them containing information that could compromise participant privacy or consent.

Authors' Contributions

EM and CC conceived of the study topic and designed and drafted the protocol. EM, MMI, CC, KRC, JW, and SW contributed to the drafting and revision of the protocol. Final revision was conducted by TH and EM.

Conflicts of Interest

EM is the managing director of CM Digital Health Solutions Ltd. CC is the inventor of NMS Assist (a digital system to help people with Parkinson monitor and manage their nonmotor symptoms at home). CC receives salary from University Hospitals Plymouth National Health Service Trust and National Institute of Health and Care Research and has received advisory, consulting, or lecture fees from AbbVie, Bial, Scient, Orkyn, Abidetex, UCB, Pfizer, EverPharma, Lundbeck, Global Kinetics, Kyowa Kirin, Britannia, and Medscape and research funding from Parkinson's UK, Edmond J Safra Foundation, National Institute of Health and Care Research, and Cure Parkinson's.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials checklist.
[DOC File , 124 KB - resprot_v11i9e40317_app1.doc]

Multimedia Appendix 2
Peer-review report (stage 1) from the Parkinson's UK - Grants for Non-Drug Approaches (London, UK).
[PDF File (Adobe PDF File), 2101 KB - resprot_v11i9e40317_app2.pdf]

Multimedia Appendix 3
Peer-review report (stage 2) from the Parkinson's UK - Grants for Non-Drug Approaches (London, UK).
[PDF File (Adobe PDF File), 2301 KB - resprot_v11i9e40317_app3.pdf]

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Abbreviations

EQ-5D-5L: EuroQol 5 Dimension 5 Level
HCP: health care professional
MDS-NMS: Movement Disorder Society–Nonmotor Rating Scale
NASSS: nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability
NHS: National Health Service
NMS: nonmotor symptoms
NMSQ: Nonmotor Symptoms Questionnaire
PDQ: Parkinson's Disease Questionnaire
PPI: patient and public involvement
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Original Paper

Information System for Symptom Diagnosis and Improvement of Attention Deficit Hyperactivity Disorder: Protocol for a Nonrandomized Controlled Pilot Study

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders during childhood; however, the diagnosis procedure remains challenging, as it is nonstandardized, multiparametric, and highly dependent on subjective evaluation of the perceived behavior.

Objective: To address the challenges of existing procedures for ADHD diagnosis, the ADHD360 project aims to develop a platform for (1) early detection of ADHD by assessing the user's likelihood of having ADHD characteristics and (2) providing complementary training for ADHD management.

Methods: A 2-phase nonrandomized controlled pilot study was designed to evaluate the ADHD360 platform, including ADHD and non-ADHD participants aged 7 to 16 years. At the first stage, an initial neuropsychological evaluation along with an interaction with the serious game developed ("Pizza on Time") for approximately 30-45 minutes is performed. Subsequently, a 2-week behavior monitoring of the participants through the mADHD360 app is planned after a telephone conversation between the participants' parents and the psychologist, where the existence of any behaviors characteristic of ADHD that affect daily functioning is assessed. Once behavior monitoring is complete, the research team invites the participants to the second stage, where they play the game for a mean duration of 10 weeks (2 times per week). Once the serious game is finished, a second round of behavior monitoring is performed following the same procedures as the initial one. During the study, gameplay data were collected and preprocessed. The protocol of the pilot trials was initially designed for in-person participation, but after the COVID-19 outbreak, it was adjusted for remote participation. State-of-the-art machine learning (ML) algorithms were used to analyze labeled gameplay data aiming to detect discriminative gameplay patterns among the 2 groups (ADHD and non-ADHD) and estimate a player's likelihood of having ADHD characteristics. A schema including a train-test splitting with a 75:25 split ratio, k-fold cross-validation with k=3, an ML pipeline, and data evaluation were designed.

Results: A total of 43 participants were recruited for this study, where 18 were diagnosed with ADHD and the remaining 25 were controls. Initial neuropsychological assessment confirmed that the participants in the ADHD group showed a deviation from the participants without ADHD characteristics. A preliminary analysis of collected data consisting of 30 gameplay sessions

showed that the trained ML models achieve high performance (ie, accuracy up to 0.85) in correctly predicting the users' labels (ADHD or non-ADHD) from their gameplay session on the ADHD360 platform.

Conclusions: ADHD360 is characterized by its notable capacity to discriminate player gameplay behavior as either ADHD or non-ADHD. Therefore, the ADHD360 platform could be a valuable complementary tool for early ADHD detection.

Trial Registration: ClinicalTrials.gov NCT04362982; https://clinicaltrials.gov/ct2/show/NCT04362982

International Registered Report Identifier (IRRID): RR1-10.2196/40189

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KEYWORDS

attention deficit hyperactivity disorder (ADHD); machine learning; web health; serious games; ADHD monitoring

Introduction

Background and Objectives

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders during childhood [1]. ADHD is commonly diagnosed during childhood and prolongs into adulthood to a variable extent ranging from 5% to 75% [2]. ADHD is characterized by persistent symptoms of inattention and hyperactivity/impulsivity that interfere with or attenuate social, academic, and occupational functioning, as well as the developmental stage. The symptoms are present prior to the age of 12 years, for a period of at least 6 months in 2 or more settings [3].

The diagnosis procedure remains challenging, as it is nonstandardized, multiparametric, and highly dependent on subjective evaluation of the perceived behavior [4,5]. Additionally, the effectiveness of treatment strategies commonly relies on systematic monitoring using pen-and-paper methods [4,6]. Subjectivity bias, difficulty monitoring in different settings, and risk of data loss are inherent obstacles to these methods.

To address the limitations of the existing approaches, ADHD360 focuses on developing an integrated technology solution that includes a serious game for a probabilistic prediction indicating the presence of ADHD in players using machine learning (ML) models and a mobile app for monitoring ADHD behaviors. The platform aims to (1) facilitate early detection of ADHD characteristics and (2) serve as an adjunct intervention for ADHD management. The first goal of the project is to analyze the gameplay behavior of the users with respect to their diagnosis (ie, ADHD or non-ADHD). Thus, discriminative gameplay patterns among the groups (ADHD or non-ADHD) are explored to estimate the users' likelihood of having ADHD characteristics. The second goal is to investigate the effectiveness of the platform as an intervention for ADHD management.

Literature Summary

Discrepancies regarding ADHD prevalence have emerged over time and among studies, leading to mixed conclusions about the possible underdiagnosis or overdiagnosis of the disorder [7]. Multiple factors have been identified to affect the recognition and diagnosis of ADHD including the parental role, school-based factors, intrinsic factors related to children, and the role of health providers [8].

In terms of the medical aspects, the access to health providers [7], limited reimbursement for specialized mental care [9], differences in clinical approaches, scoring cutoff, and factors related to the medical systems across different countries [10] have contributed to the existing difficulties in the diagnosis process. However, the underlying inconsistencies in the definition of ADHD based on different diagnostic manuals make the recognition and diagnosis of ADHD even more challenging [3,11]. Moreover, ADHD diagnosis could be biased due to the underlying subjectivity of the assessment and information interpretation procedures [12], and the lack of standardization [11].

Although diagnostic challenges could be addressed through a detailed history of prenatal conditions, family status and school/academic life [7,13], standardized tools that could enhance the diagnosis accuracy are necessary.

As early detection of ADHD could ameliorate the disorder's development, diminish its long-term impact [14], improve quality of life [15], and enhance overall functioning and self-esteem [16,17], research efforts were focused on formulating programs [14,18,19], games [20,21], or game-based tools [22,23] for early diagnosis.

For addressing the existing challenges, ADHD360 aims to develop an integrated platform comprising a serious game and a mobile app for monitoring ADHD behaviors in a SMART (Specific, Measurable, Attainable, Realistic, and Timely) way [24,25] as the core elements. The design of the serious game is based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [3] as well as neuropsychological tools. The basic principles of DSM-V and common neuropsychological tools can be easily transferred to the game design process via game mechanics implementation focusing on a specific ADHD behavior.

Methods

Study Design

A 2-phase nonrandomized controlled pilot study was performed in the context of the ADHD360 project. The protocol of the pilot trials was initially designed for in-person participation, but after the COVID-19 outbreak, it was adjusted to the new conditions imposed by the pandemic, providing remote participation. The procedures for each of these 2 ways of participation are described thoroughly below.

In-Person Participation

The first part of the pilot study begins with a first meeting between the involved members of the research team and the parents of each participant at the Laboratory of Medical Physics and Digital Innovation, School of Medicine of Aristotle University of Thessaloniki (iMedPhys). The aim of this first meeting is to thoroughly inform the parents and the children regarding the nature and scope of the project, as well as the exact procedures that take place according to the research protocol. In this context, parents can ask questions, express any concerns regarding the project, and sign the informed consent form. Afterward, the participants are subjected to a brief neuropsychological assessment by an experienced psychologist from the research team. This neuropsychological assessment includes 6 subtests of the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V), an intelligence test that measures a child's intellectual ability, and 5 cognitive domains that impact performance [26]. The 6 subtests of WISC-V used here are (1) similarities, (2) vocabulary, (3) block design, (4) figure weights, (5) digit span, and (6) coding. The main aim of this assessment is to obtain a more integrated view of the participants' general intellectual abilities in several domains such as verbal comprehension, visual-spatial perception, working memory, processing speed, and fluid reasoning. The average time to complete the subtests is approximately 48-50 minutes. If any of the participants have been assessed by this scale during the past 2 years, they are not reassessed by our research team, and the children's parents are kindly asked to provide the already existing scores of the aforementioned 6 subtests, if possible. Furthermore, the ADHD Rating Scale-IV [27] is a 4-point Likert brief questionnaire completed by the parents regarding the presence and frequency of ADHD symptoms. Inattention and hyperactivity-impulsivity are the 2 subscales integrated into the ADHD Rating Scale-IV. The total raw score of the scale is calculated by summing the scores of the 2 subscales.

Subsequently, the participants interact with the serious game "Pizza on Time" that has been specifically developed for the ADHD360 project for approximately 30-45 minutes at iMedPhys. During this interaction with the serious game, a form is completed regarding the conditions, the duration and the behaviors that will possibly be occurred. Participants interact again with the serious game for 30-45 minutes at iMedPhys, continuing from the level at which they stopped at the previous visit to complete all the levels of the first setting (the urban setting).

After the aforementioned procedures, there is a telephone conversation between the participants' parents and the psychologist who conducted the neuropsychological evaluation to discuss if there are any behaviors characteristic of ADHD that affect the daily functioning of the participants. Once the psychologist has reached a consensus with the parents that there are certain behaviors that could be observed, the behaviors are introduced into the participant's account in the mADHD360 app. Instructions regarding the installation and use of the mobile app are provided by the research team through email. The mADHD360 app can be used on a smartphone or tablet. An observation plan is scheduled, including at least 2-4 times per week of behavioral monitoring regarding the frequency or the duration of these behaviors during the time they usually spend with the participant. Each round of behavior monitoring has a duration of 12 minutes. The duration of this phase is determined to be 2 weeks. During the behavior monitoring phase, the participants do not interact with the serious game.

Once behavior monitoring is complete, the research team instructs the participants to continue playing the game using the second (jungle) and third (space) settings on the premises of iMedPhys. The mean duration of this part is 10 weeks with a frequency of at least 2 times a week, depending on the participants' availability. In this second part of the pilot testing phase, the goal is to exploit the serious game as an intervention to improve certain ADHD symptoms.

Next, a second round of behavior monitoring is performed following the same procedures as the previous one. Furthermore, a neuropsychological assessment is conducted following the same procedures as those during the first evaluation in the beginning of their participation.

Remote Participation

All the procedures are identical to those followed during in-person participation, apart from the interactions with the serious game that are done remotely from their home using their personal computers.

Participant Selection

The eligibility criteria were reviewed by a member of the research team before assignment to the study. Textbox 1 lists the inclusion and exclusion criteria for enrollment into the study.

Textbox 1. Inclusion and exclusion criteria for participant enrollment.

Inclusion criteria

- Participants should be between 7 and 16 years old.
- Participants of the attention deficit hyperactivity disorder (ADHD) group should be diagnosed by an approved body of the Ministry of Health.
- Participants should be willing to follow the study protocol and procedures.
- The ADHD symptoms should not be attributed to organic disease.
- Parents must voluntarily provide written consent for their child's participation in the study.

Exclusion criteria

- Participants suffering from comorbid conditions other than ADHD are excluded.
- Children whose parents are not willing to provide written consent for participation in the study are excluded.

All participants are comprehensively informed regarding the procedures of the study through a document named "Participant Information and Consent Form." Moreover, the participants are informed about the purpose of the study as well as the following aspects of their participation:

- Their participation is voluntary.
- They can ask questions about the study procedures before participating in the study.
- They will be aware of the underlying risk or burden associated with their participation.
- They will know who will benefit from conducting this research.
- They will know how data collection and data protection will be performed during the project's lifetime as well as whether data will be destroyed or reused (in case there is a possibility to reuse them).
- They will be fully informed, and they will agree for further use of their data.
- They can leave the study at any time and withdraw their data from the study.
- They will be aware of the possible commercial exploitation of the research findings.

Each informed consent is signed by the researcher who informs the participant and the principal investigator of the study. The informed consent explicitly states that the study was approved by the Committee for Bioethics and Ethics of the Medical School at the Aristotle University of Thessaloniki and all personal details are anonymized using a unique user identification code.

Ethics Approval

The study protocol (trial registration: NCT04362982) was approved by the Ethics and Bioethics Committee of the School of Medicine at the Aristotle University of Thessaloniki (reference number: 6.225/29.7.2020).

Recruitment of Participants

We initially considered recruiting at least 20 participants (10 ADHD and 10 non-ADHD) in our pilot trials. We estimated the sample size for the definite study by performing power analysis using GPower software (version 3.1, Universität Düsseldorf). We conducted a paired *t* test analysis using a power of 0.8, a significance level of 0.05, and an effect size equal to 0.2. The total sample size was estimated to be 199 participants. As proposed by Billingham et al [28], the sample size in pilot trials does not need calculation but needs justification. Thus, recruiting a small number of participants seems sufficient according to the suggestions of Stallard [29] and is similar to what was proposed by Julious [30].

The ADHD group is mainly composed of patients from the Community Center for Mental Health of Children and Adolescents at the General Hospital of Thessaloniki "G. Papanikolaou," which supports the implementation of pilot trials. Furthermore, dissemination activities such as social media posts, mass media interviews, information events open to the public, and project presentations at conferences and workshops are considered essential to recruit participants for pilot trials.

ADHD360 Platform Design

The ADHD360 platform consists of 2 main components, a serious game and a mobile app for behavior monitoring.

Serious Game for ADHD

Game design covers a wide range of activities in designing games, including story, aesthetics, mechanics, and technology [31]. These variables have to be carefully considered for successful game design. Hunicke et al [32] propose the mechanics-dynamics-aesthetics framework and define game mechanics as the "mechanisms that describe the specific elements of the game, at the level of data presentation and algorithms (...), also the mechanics relate to the behaviors and control mechanisms provided to the player in the game context."

The mechanics-dynamics-aesthetics framework standardizes the basic components of a game into distinct parts such as rules, systems, and fun. This distinction helps us in the design of the mechanisms because the basic components of the game can be translated into game design elements such as mechanics, dynamics, and aesthetics that are visible to both the end users and the game designer, but from different perspectives. There are some games that have been developed specifically to improve ADHD symptoms, whereas commercial game titles have also been used for research purposes to measure the performance of users with or without ADHD diagnosis [33].

The 2 games that focus on improving ADHD symptoms are Plan it Commander [34] and Antonyms [35]. The 2 major gaps

in existing research are the (1) interconnection of the game mechanics with the diagnostic criteria according to DSM-V and (2) correlation of user performance with the standard results of ADHD tests through ML algorithms.

For bridging this gap, we focused on developing a serious game called “Pizza on Time” (Figure 1), which is a runner game. The player tries to avoid obstacles and collect coins to deliver the pizza, and each time the player hits an obstacle, a pizza slice is lost. When all the pizza slices are lost, the player needs to start over at the same level. There are 3 different in-game world levels (city, jungle, and space) with a total of 120 predefined sublevels. Additionally, 4 mini games were integrated with the main runner game to enrich the existing mechanics, retaining the concept of pizza delivery.

Figure 1. Screenshot of the “Pizza on Time” game.

Mobile App for Behavior Monitoring

The ADHD360 monitoring app (mADHD360) developed in the project provides teachers, parents, and health professionals with features to easily monitor specific targeted behaviors related to ADHD. Although several related information and communications technology solutions were implemented to replace traditional pen-and-paper observation charts in the past years [24], not all of them were successful [6]. The mADHD360 app differs from other digital monitoring apps, which are mainly based on pre-existing traditional forms of assessment. Instead, the app addresses the need to include the range of observation features needed to conduct a complete functional behavioral assessment in a unique and an easy-to-use tool. Finally, it allows teachers, parents, and clinicians to use a sociocentric technology to create a network of people and develop and monitor a behavioral intervention plan that is shared among all people involved in the care of the child with ADHD.

The process of creating a new subject profile and monitoring behavior can be described as follows:

First, the associate user (usually one of the parents) creates an account and enters the basic data of the subject to be monitored in the mADHD360 app. There is a strict policy regarding the sensitive personal data of the children; it does not allow real names to be used or any other significant detail that can reveal the identity of the children in the real world.

The next step is to create a network of people, usually people that spend time with the child (such as a relative or a class teacher) and a health professional. The app supports a directory of ADHD experts, which can be added to the child’s observation network. Inviting other people is a very simple process, and it can be performed via email.

A limited number of ADHD-related behaviors are associated with the child. The associations come from a predefined vocabulary [36], but the user can also enter custom behaviors. The network of people can gather data to unveil the function of a child‘s behavior and plan an intervention to reduce or eliminate the undesirable behavior with the help of a health professional. Data are gathered in sessions, and for each behavior, the app can monitor the frequency and duration. Usually, there are 2

rounds of monitoring, 1 before the intervention and the other during or even after the intervention.

Finally, the efficacy of each treatment can be evaluated by health professionals through visual analysis of the data gathered by the network members during the assessment periods.

The mADHD360 app is based on the Web Health Application for ADHD Monitoring (WHAAM) [36]; although the basic principles are retained, the latter is enhanced with more features, such as asynchronous chat capabilities, and offers advanced usability and user experience.

From a technology point of view, the mADHD360 app is designed to run on mobile devices, smartphones, and tablets. It is delivered for free as a progressive web app with the main game.

Analysis

Statistical Analysis

Statistical analysis is performed using SPSS (version 26.0, IBM Corp) and the statistical significance level is set at P=.05. Continuous variables are explored for normality by the Shapiro-Wilk test to calculate the appropriate descriptive statistics. Continuous variables that are approximately normally distributed are reported as means (SDs) whereas those that are not normally distributed as medians and IQRs (Q1-Q3, where Q1 and Q3 are the first and the third distribution quartiles, respectively). Neuropsychological data expressed as raw scores are treated as continuous variables. Categorical data are described as frequencies and percentages.

ML Methodology

State-of-the-art ML algorithms are used to analyze labeled gameplay data. Specifically, we attempt to classify game-generated data based on the user's known label (ADHD or non-ADHD). All in-game events of a gameplay session are recorded to form a time series that one can use to reconstruct the whole gameplay session. These events correspond to player actions and environmental parameters, such as performing a jump/move, left or right moving action, obstacle collision, and coin collection. Informative feature extraction is performed by splitting players' time series depending on the game level. Different feature extraction techniques are assumed for each level depending on its type. In the main runner game, several aggregates are calculated by capturing different events during the gameplay (ie, movement of a player or the ability to avoid obstacles). In the mini games, feature extraction is based on the characteristic game mechanics and events of the respective mini game. The final feature vector of each player is produced by concatenating the individual-level feature vectors.

A schema that includes train-test splitting with a 75:25 split ratio, *k*-fold cross-validation (CV) with k=3, an ML pipeline, and data evaluation was designed for experimental purposes. The train-test splitting is used for model specification (eg, feature selection and model tuning), model selection, and training of the final model. Modeling decisions are made on the training set. Thus, the test set is used only to evaluate and report the statistics of the algorithm's performance. The purpose of 3-fold CV is to fine-tune the hyperparameters of the supervised learning algorithms (classifiers) that we investigate.

For each classifier, an ML pipeline was designed to include the following procedures: (1) removal of features with 0 variance, (2) univariate feature selection according to a statistical criterion (ANOVA F value between label and feature), (3) principal component analysis for dimensionality reduction, and (4) classifier training. Therefore, the hyperparameters of all the steps are tuned (eg, the number of components in principal component analysis) in the 3-fold CV process. The *F1* score is used as the optimization criterion in the 3-fold CV, and the best configuration of each method's pipeline is then used on the entire training set (fully trained pipeline).

Next, the algorithm with the best-performing pipeline in the 3-fold CV is selected as the proposed method. The general performance of our system on unlabeled data is estimated by evaluating the predictive performance of the proposed method that consists of a fully trained pipeline on the test set. The performance of the ML system is also evaluated based on methods other than the proposed one. The following learning algorithms were applied: k-nearest neighbors (kNN) [37], logistic regression (LogReg) [38], support vector machine (SVM) [39], random forest (RF) [40], ridge classifier (RC) [41], passive aggressive classifier (PAC) [42], stochastic gradient descent (SGD) [43], and naïve Bayes (NB) [44]. For each classifier, we tuned its most important parameters using grid-search CV on a sufficient range of parameter values. The objective of the optimization is to maximize the micro-*F1* score across all validation folds. In addition, we report the performance metrics of accuracy, precision, recall, and *F1* scores.

Results

Demographics

In total, 43 participants were recruited with a mean age of 11.82 (SD 2.81) years. Among these, 28 (65%) were male and 15 (35%) were female. Of the 43 participants, 18 (42%) were diagnosed with ADHD and 25 (58%) participants were considered controls (non-ADHD). Approximately 30 participants (70%) completed the first part of the pilot phase remotely.

Neuropsychological Data

Neuropsychological data were obtained from 30 participants. They were evaluated using WISC-V by the psychologist of the ADHD360 team or by an approved national body within the last 2 years. Among the 30 participants, 10 (33%) were diagnosed with ADHD and 20 (67%) were considered as healthy controls (non-ADHD). There were 21 males (70%) and 9 females (30%). In the ADHD group, all participants were male, whereas in the non-ADHD group, 11 (55%) were male and 9 (45%) were female. The mean age of the screened participants was 11.40 (SD 2.85) years. In the ADHD group, the mean age of the participants was 12.90 (SD 2.64) years, whereas that of the participants in the non-ADHD group was 10.65 (SD 2.70) years.

According to the data from the first neuropsychological assessment, the mean score in the figure weights subtest in the ADHD group was 14.00 (SD 5.79), whereas the median score of this subtest in the non-ADHD group was 19 (IQR 13-24). The mean scores in the subtests block design, similarities, digit span, coding, and vocabulary are presented in Table 1.

The mean score of the participants in the inattention subscale of the ADHD Rating Scale-IV was 12.70 (SD 7.04), whereas that in the hyperactivity-impulsivity subscale was 10.97 (SD 6.65). In the full group of participants, the mean total score was 23.67 (SD 12.56). The mean scores on the ADHD Rating Scale-IV obtained by grouping the participants based on their diagnosis are presented in Table 2.

Table 1. Mean scores of the study participants in the subtests block design, similarities, digit span, coding, and vocabulary.

WISC[a] subtest	ADHD[b], mean (SD)	non-ADHD, mean (SD)
Block design	19.60 (4.30)	22.85 (8.02)
Similarities	22.00 (7.45)	23.50 (9.05)
Digit Span	18.30 (4.03)	19.75 (6.26)
Coding	27.80 (9.69)	32.20 (13.46)
Vocabulary	20.20 (5.55)	23.05 (8.17)

[a]WISC: Wechsler Intelligence Scale for Children.

[b]ADHD: attention deficit hyperactivity disorder.

Table 2. Mean scores of the participants on the ADHD Rating Scale-IV.

ADHD[a] Rating Scale-IV	ADHD, mean (SD)	non-ADHD, mean (SD)
Inattention subscale	18.50 (5.84)	9.80 (5.74)
Hyperactivity-impulsivity subscale	15.30 (6.58)	8.80 (5.67)
Total score	33.80 (9.94)	18.60 (10.62)

[a]ADHD: attention deficit hyperactivity disorder.

Gameplay Data

Following the methodology described above, we present the results of a preliminary analysis of gameplay data collected during pilot trials. Gameplay data were collected from all recruited participants. However, technical difficulties (ie, unstable internet connection and game installation issues) led to insufficient or no data generation in 13 of the 43 participants (30%). Therefore, gameplay data collected from 30 (70%) participants were used in the following preliminary analysis. We comprehensively describe the CV results for a training set consisting of data collected from 22 of the 30 participants (73%) as well as the selection of the best model. Subsequently, we evaluate the predictive performance on a test set consisting of data gathered from 8 (27%) participants using point estimates and CIs.

A graphical illustration of the CV *F1* results for each learning method is shown in Figure 2. Furthermore, detailed results of the *F1* score and the other performance measures for the CV procedure are given in Table 3.

Most classifiers achieved an *F1* score above 0.5. We observed significant overfitting for RF, kNN, and NB, with a difference of 0.1 between the training and validation scores. The test performance scores are given in Table 4.

The previously mentioned models seem to be substandard solutions for this classification problem, with all of them dominated by LogReg, SGD, SVM, and PAC. The latter models feature a tradeoff between validation performance and goodness of fit. Among these methods, we selected SVM for the following reasons: (1) It achieves the highest validation *F1* score (0.66). (2) Although SGD achieves the same validation score as SVM, the latter also achieves a better fit with a difference of approximately +0.07 between training and validation, which is approximately –0.09 for the former.

Even though the results are indicative of the potential that ML has in the domain of ADHD prediction based on gameplay data, we presume that experimenting with a larger data set could give more accurate and concrete conclusions.

Figure 2. Cross-Validation F1 scores. SGD: stochastic gradient descent.

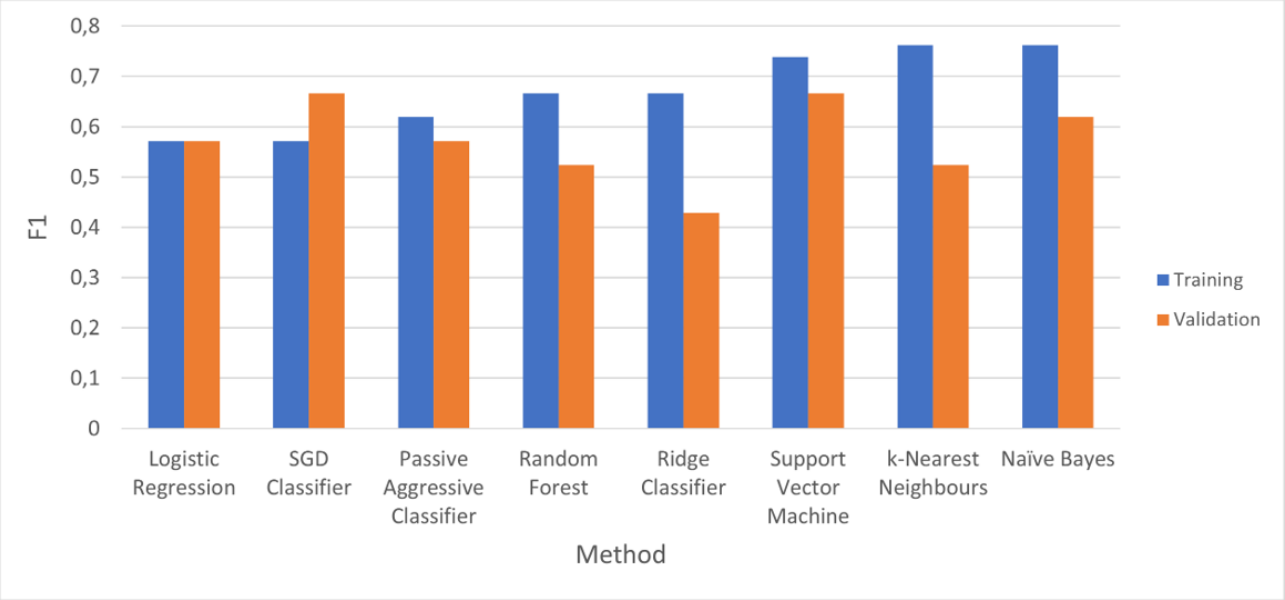

Table 3. Cross-validation results.

Method	Accuracy		Precision		Recall		*F1*	
	Training	Validation	Training	Validation	Training	Validation	Training	Validation
NB[a]	0.7619	0.6190	0.7011	0.5556	0.8333	0.7778	0.7619	0.6190
k-NN[b]	0.7619	0.5238	0.7083	0.4500	0.7778	0.5556	0.7619	0.5238
LogReg[c]	0.5714	0.5714	0.0000	0.0000	0.0000	0.0000	0.5714	0.5714
PAC[d]	0.6190	0.5714	0.5337	0.5000	0.8333	0.8889	0.6190	0.5714
RF[e]	0.6667	0.5238	0.5935	0.4444	0.7222	0.5556	0.6667	0.5238
RC[f]	0.6667	0.4286	0.6074	0.3833	0.6667	0.5556	0.6667	0.4286
SGD[g]	0.5714	0.6667	0.4932	0.5667	0.6667	1.0000	0.5714	0.6667
SVM[h]	0.7381	0.6667	0.7238	0.5833	0.6667	0.6667	0.7381	0.6667

[a]NB: naïve Bayes.
[b]k-NN: k-nearest neighbors.
[c]LogReg: logistic regression.
[d]PAC: passive aggressive classifier.
[e]RF: random forest.
[f]RC: ridge classifier.
[g]SGD: stochastic gradient descent.
[h]SVM: support vector machine.

Table 4. Evaluation of test results.

Method	Accuracy		Precision		Recall		*F1*	
	CI	Test	CI	Test	CI	Test	CI	Test
NB[a]	0.14-0.85	0.42	0.14-0.85	0.42	1.00-1.00	1.00	0.25-0.92	0.60
k-NN[b]	0.14-0.71	0.42	0.00-1.00	0.33	0.00-1.00	0.33	0.00-0.67	0.33
LogReg[c]	0.14-0.85	0.42	0.14-0.85	0.42	1.00-1.00	1.00	0.25-0.92	0.60
PAC[d]	0.13-0.71	0.28	0.13-0.75	0.33	0.23-1.00	0.66	0.23-0.83	0.44
RF[e]	0.28-0.85	0.57	0.15-1.00	0.50	0.23-1.00	0.66	0.23-0.90	0.57
RC[f]	0.27-0.85	0.57	0.00-1.00	0.50	0.00-1.00	0.66	0.00-0.88	0.57
SGD[g]	0.14-0.71	0.42	0.00-1.00	0.33	0.00-0.76	0.33	0.00-0.66	0.33
SVM[h]	0.71-1.00	0.85	0.50-1.00	0.75	1.00-1.00	1.00	0.66-1.00	0.85

[a]NB: naïve Bayes.

[b]k-NN: k-nearest neighbors.

[c]LogReg: logistic regression.

[d]PAC: passive aggressive classifier.

[e]RF: random forest.

[f]RC: ridge classifier.

[g]SGD: stochastic gradient descent.

[h]SVM: support vector machine.

Discussion

Limitations of the existing screening procedures for ADHD diagnosis are summarized as high dependence on pen-and-paper practices, subjectivity bias, difficulty in monitoring in different settings, and risk of data loss. The ADHD360 platform, consisting of the serious game “Pizza on Time” and the mADHD360 app, attempts to offer a holistic technological solution for early detection of ADHD characteristics and serve as a training tool against ADHD-related symptoms. It facilitates real-time data collection in different settings and from different individuals involved in the user’s care. Moreover, the ADHD360 platform enables quantitative data analysis assessing the behavior and game performance of the user while providing a more integrated view of the user's behavioral characteristics. Investigating different state-of-the-art ML methods revealed that our platform is characterized by a notable capacity to discriminate players based on their in-game patterns as those who have ADHD characteristics and those who do not. Thus, it is expected to serve as a complementary screening tool benefiting health care professionals, educators, and people with ADHD.

However, the health emergency imposed by COVID-19 affected the implementation of pilot trials by forcing adaptation of the protocol to remote conditions. Moreover, lockdowns and social distancing may have contributed to the low sample size and the high number of dropouts during the study. Additionally, the long duration of the experimental protocol and the need for commitment to the study procedures may have negatively affected users’ adherence to pilot trials. Moreover, ADHD has been characterized by “a dislike of mental effort” [45]. Considering the aforementioned limitations, we recruited about twice as many participants as originally intended. However, the dropout rate was approximately 30% (13 participants), as 30 participants (70%) completed the first part of pilot phase remotely.

Even though preliminary analyses of the collected data have shown promising results, the platform can be further improved by training the ML models on a larger data set that can be developed by recruiting more participants. This would allow the learning models to further improve their accuracy in correctly distinguishing ADHD gameplay behaviors from non-ADHD gameplay behaviors. The monitoring app will soon have a dedicated enrollment service for health experts; parents will be able to see a list of related professionals near their area and contact a person to join their child’s network. Moreover, we will add asynchronous chatting capabilities and a strict schedule-monitoring functionality, with device and calendar notifications. The “Pizza on Time” game is planned to be released to the public for both Android and iOS devices, as well as for PCs (Windows and Mac).

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report by the Special Management Service for the Competitiveness, Entrepreneurship and Innovation Operational Programme (Ειδική Υπηρεσία Διαχείρισης Επιχειρησιακού Προγράμματος Ανταγωνιστικότητα Επιχειρηματικότητα και Καινοτομία (ΕΥΔ ΕΠΑνΕΚ)) - Special Service for the Management of Implementation of Research, Technological Development and Innovation Activities (Ειδική Υπηρεσία Διαχείρισης και Εφαρμογής Δράσεων στους τομείς Έρευνας, Τεχνολογικής Ανάπτυξης και Καινοτομίας (ΕΥΔΕ ΕΤΑΚ)) (Greece).
[DOCX File , 186 KB - resprot_v11i9e40189_app1.docx]

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Abbreviations

ADHD: attention deficit hyperactivity disorder
CV: cross-validation
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
iMedPhys: Medical Physics and Digital Innovation, School of Medicine of Aristotle University of Thessaloniki
kNN: k-nearest neighbors
LogReg: logistic regression
ML: machine learning
NB: naïve Bayes
PAC: passive aggressive classifier
RC: ridge classifier
RF: random forest
SGD: stochastic gradient descent
SVM: support vector machine
WISC-V: Wechsler Intelligence Scale for Children, Fifth Edition

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Protocol

Developing Clinical Artificial Intelligence for Obstetric Ultrasound to Improve Access in Underserved Regions: Protocol for a Computer-Assisted Low-Cost Point-of-Care UltraSound (CALOPUS) Study

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Abstract

Background: The World Health Organization recommends a package of pregnancy care that includes obstetric ultrasound scans. There are significant barriers to universal access to antenatal ultrasound, particularly because of the cost and need for maintenance of ultrasound equipment and a lack of trained personnel. As low-cost, handheld ultrasound devices have become widely available, the current roadblock is the global shortage of health care providers trained in obstetric scanning.

Objective: The aim of this study is to improve pregnancy and risk assessment for women in underserved regions. Therefore, we are undertaking the Computer-Assisted Low-Cost Point-of-Care UltraSound (CALOPUS) project, bringing together experts in machine learning and clinical obstetric ultrasound.

Methods: In this prospective study conducted in two clinical centers (United Kingdom and India), participating pregnant women were scanned and full-length ultrasounds were performed. Each woman underwent 2 consecutive ultrasound scans. The first was a series of simple, standardized ultrasound sweeps (the CALOPUS protocol), immediately followed by a routine, full clinical ultrasound examination that served as the comparator. We describe the development of a simple-to-use clinical protocol designed for nonexpert users to assess fetal viability, detect the presence of multiple pregnancies, evaluate placental location, assess amniotic fluid volume, determine fetal presentation, and perform basic fetal biometry. The CALOPUS protocol was designed using the smallest number of steps to minimize redundant information, while maximizing diagnostic information. Here, we describe how ultrasound videos and annotations are captured for machine learning.

Results: Over 5571 scans have been acquired, from which 1,541,751 label annotations have been performed. An adapted protocol, including a low pelvic brim sweep and a well-filled maternal bladder, improved visualization of the cervix from 28% to 91% and classification of placental location from 82% to 94%. Excellent levels of intra- and interannotator agreement are achievable following training and standardization.

Conclusions: The CALOPUS study is a unique study that uses obstetric ultrasound videos and annotations from pregnancies dated from 11 weeks and followed up until birth using novel ultrasound and annotation protocols. The data from this study are being used to develop and test several different machine learning algorithms to address key clinical diagnostic questions pertaining to obstetric risk management. We also highlight some of the challenges and potential solutions to interdisciplinary multinational imaging collaboration.

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KEYWORDS

ultrasound; obstetrics; artificial intelligence; machine learning; data annotation

Introduction

Background

Every year between 250,000 and 300,000 women die during pregnancy or following childbirth, and approximately 2.5 million neonates die within the first 28 days of life [1]. Most of these deaths occur in low-resource settings and can be prevented by timely access to evidence-based interventions. To help mitigate these deaths and the associated large burden of morbidity, the World Health Organization recommends a package of antenatal care [2] that includes an ultrasound before 24 weeks of gestation. The recommendations for the antenatal ultrasound are to assess fetal cardiac activity, fetal number and chorionicity, gestational age and fetal size, placental appearance and location, and a basic anomaly screen [2]. In addition to early screening, routine assessment of fetal malpresentation near term is also effective in reducing morbidity and mortality [3].

Significant barriers remain to the universal access to antenatal ultrasound. Primarily, these are related to procuring and maintaining ultrasound equipment and a lack of trained personnel [4]. The first of these barriers is being addressed through technological advances in low-cost, handheld ultrasound devices, making point-of-care ultrasound more accessible. However, implementation remains limited due to insufficient numbers of trained health care providers. In addition, training in obstetric ultrasound is lengthy, costly, and difficult to scale up. Several research efforts have described how teleradiology or automated solutions might overcome these obstacles through the use of simple obstetric ultrasound protocols using portable devices [5-10].

Objectives

To contribute to the improvements in antenatal care and pregnancy risk assessment for women in low-resource settings, we are undertaking the Computer-Assisted Low-Cost Point-of-Care UltraSound (CALOPUS) project. This brings together experts in machine learning and clinical obstetric ultrasound in an international collaboration (Multimedia Appendix 1). The aim of this study is to develop and evaluate simple-to-use clinical protocols and machine learning–based decision-making tools for nonexpert users, which are designed to be functionally suitable for implementation at scale in underserved regions.

In this paper, we describe our approach to working toward automating the requirements of a basic ultrasound examination [2,11]. Well-designed acquisition and curation of data and their careful annotation are crucial in such studies. The aims of this paper are to report the development of optimal clinical acquisition and image annotation protocols suitable for automated analysis and to describe our experience and share learning regarding ultrasound video acquisition and annotation in a multisite setting.

Methods

Study Overview

The ultimate objective of the CALOPUS study is to develop machine learning models based on simplified obstetric ultrasound to predict pregnancy risk factors, such as the detection of noncephalic presentation or a low-lying placenta. The primary objectives of this phase of CALOPUS are as follows:

1. To develop an optimal clinical acquisition protocol suitable for automated analysis that can be obtained by a minimally trained health care provider
2. To capture ultrasound videos and perform video annotation to develop a data set suitable for machine learning
3. To advance capabilities in real-time ultrasound video partitioning to prevent fetal sex determination, which is an important prerequisite for the global dissemination of ultrasound

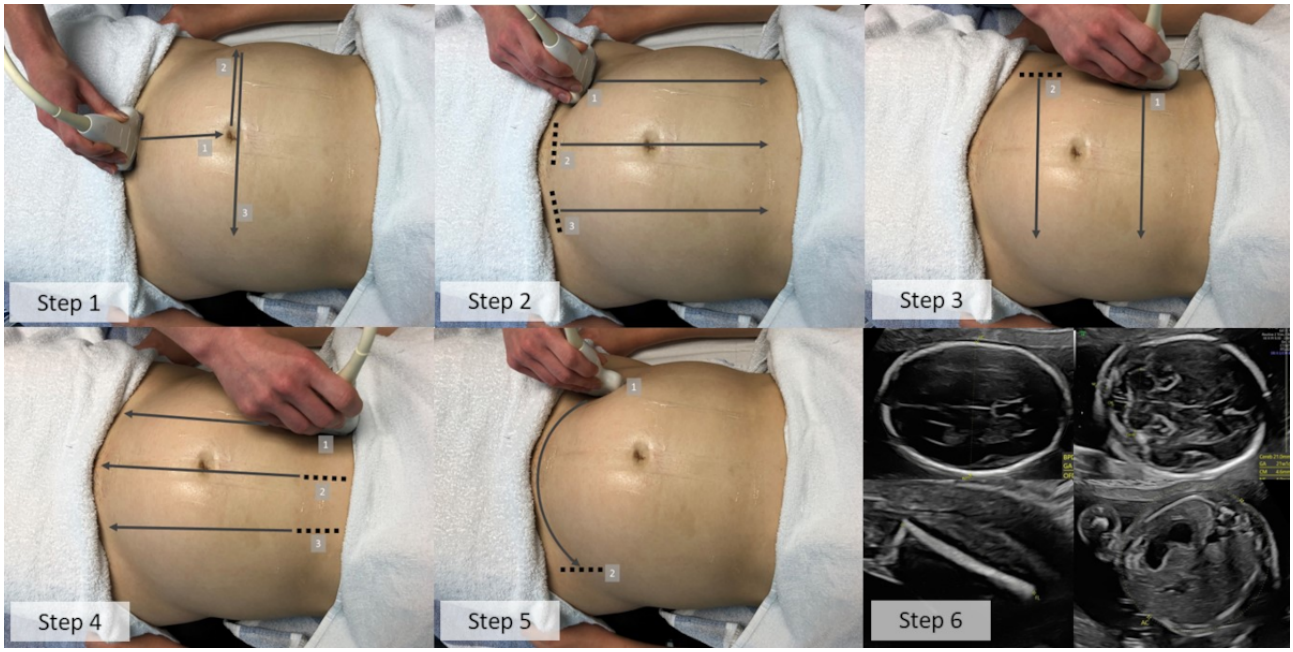
This prospective study is an interdisciplinary international collaboration among the Translational Health Science and Technology Institute, Delhi, India; the Civil Hospital, Gurugram, Haryana, India; the Institute of Biomedical Engineering and the Nuffield Department of Women's and Reproductive Health, University of Oxford, United Kingdom; and the Women's Centre, John Radcliffe Hospital, Oxford, United Kingdom.

Setting, Study Design, and Participants

In the 2 hospitals, the participating pregnant women were scanned in a room set up with an ultrasound machine configured to record full-length scans by screen capture. Each woman underwent 2 consecutive ultrasound scans. The first was our CALOPUS protocol, which consists of a series of simple, standardized ultrasound sweeps (Figure 1), immediately followed by a routine, full clinical ultrasound examination that served as the comparator. All scans were performed by trained sonologists (both sonographers and medical doctors trained in obstetric ultrasound) on identical GE Voluson E8 (General Electric Healthcare) ultrasound machines using C2-9 or C1-5

curvilinear probes. All data were anonymized at the point of collection using specifically designed video capture software that blanks out the patient identifiable information on the screen recording.

Figure 1. The Computer-Assisted Low-Cost Point-of-Care UltraSound protocol, developed on the basis of the studies described (see text).



The enrollment of participants, clinical data collection, and the ultrasound scans (CALOPUS and routine clinical scans) were performed by a dedicated clinical research team of doctors, nurses, and sonologists. All women were eligible if they were able to provide informed consent, were aged ≥18 years, and had (or were attending for) a scan between 11 and 14 weeks of pregnancy for gestational age assessment based on fetal crown-rump length (CRL).

In India, participants were recruited from the ongoing interdisciplinary Group for Advanced Research on BirtH outcomes–Department of Biotechnology India Initiative (GARBH-Ini) cohort [12]. This is a prospective observational cohort of pregnant women enrolled before 20 weeks of gestation. All pregnant women were followed up during pregnancy with ultrasound scans at 18 to 20, 30 to 32, and 35 to 37 weeks of gestation, and birth outcomes were determined. At Oxford, women attending the antenatal ultrasound department of the John Radcliffe Hospital were invited to enroll throughout pregnancy from 11+0 weeks of gestation. Consecutive recruitment was up to a weekly quota of 20 scans per week and could be targeted to better focused recruitment of women in specific gestational age windows.

As the incidence of breech presentation reduces to approximately 3% to 4% at term [13], the anticipated number of scans recorded of noncephalic presenting fetuses would inevitably be small, even in a large data set. As machine learning models require a degree of balance in the training data set, to ensure a higher proportion of ultrasound scans in women with noncephalic fetal presentation, women in the Indian cohort with a noncephalic fetus at the 30 to 32 or 35 to 37 weeks scan received additional scans every 15 days until the presentation became cephalic or until delivery.

Ethics Approval

In India, ethics approval was obtained from the institutional ethics committees of the Translational Health Science and Technology Institute, Faridabad, India, THS/1.8.1/(71), dated August 26, 2019, and Gurugram Civil Hospital, Haryana, India, GHG/IEC letter, dated September 3, 2019. Written informed consent was obtained from all study participants by the study nurses under the supervision of research officers. For illiterate women, the details of the study were explained in the presence of a literate impartial witness. Verbal consent and thumb impressions were taken from the participants along with the signature of the witnesses.

In the United Kingdom, approval from the West of Scotland Research Ethics Committee 5 (reference 18/WS/0051) was obtained, along with approvals from the Health Research Authority and Oxford University Hospitals. Trained research midwives or the sonologists themselves completed the consent process with participants, and written informed consent was obtained.

Defining the CALOPUS Scan Acquisition Protocol

Due to the exploratory nature of this collaboration, the protocol for scan acquisition developed over time. In 2016, Abuhamad et al [11] published a clinical study validating the feasibility and accuracy of a 6-step approach to performing a focused basic obstetric ultrasound. Each step corresponds to an integral part of prenatal care and helps identify women at high risk of obstetric complications. For example, in a setting with poor health care and transport infrastructure, it would be ill-advised for a woman to attempt a vaginal breech birth or delivery of twins without access to comprehensive emergency obstetric care facilities. Similarly, a woman with known major placenta previa should be delivered by cesarean section and not attempt vaginal birth. The purpose of this 6-step approach was to provide

a simple framework that could be readily taught to health care providers with limited scanning experience. A series of 5 simple steps allows the evaluation of fetal presentation, presence of cardiac activity (fetal viability), presence of multiple pregnancies, determination of placental location, and amniotic fluid measurement. The sixth step is a standard clinical freehand scan for fetal biometry.

This 6-step approach was adopted as the initial scanning protocol for the CALOPUS. However, although a protocol for human point-of-care ultrasound benefits from sequential decision-making, it contains overlap and redundant information, that is, each step contains information relevant to more than one of the six aims. A hypothesis of this study is that automation offers the opportunity to optimize the scanning protocol to reduce redundancy in overlapping scan sweeps. To test this hypothesis, we conducted an initial analysis of 470 videos from the first 80 participants. All women had viable second or third trimester pregnancies (gestational age range from 19+3 to 40+0 weeks).

Clinical Protocol Refinement to One Optimized for Machine Learning

On the basis of this, the original 6-step approach was modified into the CALOPUS ultrasound protocol (Figure 1 and Multimedia Appendix 2). Steps 1 and 5 of the original approach were removed to streamline the acquisition process. Hence, the original step 2 became the new step 1 of the CALOPUS ultrasound protocol, as it consistently confirmed both fetal presentation and viability.

Steps 2 and 3 of the CALOPUS ultrasound protocol were from the original 6-step approach and aim to identify multiple pregnancies and quantify amniotic fluid**.** We used maximum vertical pool (MVP) depth to assess amniotic fluid volume (rather than the amniotic fluid index due to its simplicity), as neither have been demonstrated to be superior in predicting adverse outcome. Another reason to use MVP depth was that amniotic fluid index results in a higher number of diagnoses of oligohydramnios than MVP depth, which in turn may result in an increased number of inductions of labor and cesarean sections but without benefits to perinatal outcomes [14,15].

Even in combination with other steps, step 4 of the original 6-step approach was found to be inadequate for determining the relationship between the placenta and the cervix, because the cervix is not always directly behind the pubic symphysis. This is important, as clinically, a low-lying placenta is ruled out by measuring the distance from the placental margin to the internal cervical os. It is widely accepted that an anterior placenta will not impede vaginal delivery if it is more than 10 mm from the internal os during the second trimester. It has been recommended that the posterior placenta should be >15.5 mm from the internal os in the second trimester [16]. Hence, a new step (step 5 of the CALOPUS ultrasound protocol) was introduced to improve visualization of the uterine lower segment and cervix and to reduce the number of false positive cases (where the placenta is not low-lying but is suspected to be so). This was a U-shaped sweep from the right to the left iliac fossa, along the maternal pelvic brim.

The final step of the CALOPUS ultrasound protocol (step 6) is a validation step to measure the CRL if <14 weeks gestation or the head circumference, transcerebellar diameter, biparietal diameter, abdominal circumference, femur length, and the deepest pool of amniotic fluid if ≥14 weeks (CRL>84 mm [17]) according to previously described ultrasound methodology [18-20]. This was done so that any measurable biometry planes were identified from steps 1 to 5 of the CALOPUS ultrasound protocol, and biometric measurement values were compared with the paired standard clinical ultrasound. The methodology for measuring fetal biometry and amniotic fluid remained constant across all acquisition protocol iterations, with the use of a standardized protocol from international standards [20,21] to ensure the quality control of the images obtained.

Statistical Justification

A pilot study was conducted to calculate the sample size required to answer the following questions:

1. Does the addition of step 5 of the CALOPUS ultrasound protocol help to visualize the cervix more than step 4 of the CALOPUS ultrasound protocol alone?
2. Does the fullness of the bladder have more of an impact on visualization of the cervix than the addition of step 5 of the CALOPUS ultrasound protocol?
3. Is the addition of step 5 of the CALOPUS ultrasound protocol clinically significant?

The pilot study focused on women between 18 and 22 weeks of gestation, because at this gestation, it should be possible to confirm placental location with transabdominal scanning alone. At more advanced gestations, a transvaginal scan is often necessary to check the distance between the placental margin and cervix, particularly when the placenta is posterior and within the lower segment of the uterus. The pilot study was a paired cohort study in which data were analyzed using McNemar test (a 2-sample paired-proportions test) performed in STATA (version 16.1). A total of 69 women underwent both steps 4 and 5 of the CALOPUS ultrasound protocol. The cervix was defined as having been seen if part of the endocervical canal was visible, and the bladder was well filled if it contained >200 mL of urine as defined by a cuboid volumetric calculation. This recommendation for bladder fullness is based on guidance for placental imaging, because a full bladder stretches out the lower segment to provide a more realistic idea of the relationship between the placental edge and the cervix or any previous cesarean scar [22].

The sample sizes were calculated using type 1 error rate of 0.05 and 90% power. A sample size of 212 scans was needed to detect the differences observed in the pilot study between the addition of steps 5 and 4 of the CALOPUS ultrasound protocol alone or the contribution of a full bladder in correctly diagnosing the placental location, compared with a freehand scan gold standard.

Data Processing

The ultrasound machine video output port was split at both sites. One port was connected to an image-acquisition hardware installed on a desktop computer. Data collection software was implemented to control the image-acquisition hardware and to

collect the ultrasound videos in real time, without affecting the scanning procedure. The recordings were saved locally on a desktop computer.

Data Quality Checks and Storage

Scans underwent manual quality checking for the following reasons:

- To assess whether all the scans have synced properly from the clinical site
- To assess if the ultrasound signal had been successfully captured in the video
- To assess if any steps or sweeps were missing from the scan directory
- To record the duration of the video files
- To undertake a basic visual check of video quality (eg, image corruption or distortion).

The scans were then transferred to the server for annotation and subsequent analysis at each site.

Annotation Protocol

The annotation of key anatomical structures in the CALOPUS ultrasound protocol video sweeps are used alongside the video as the training input to the machine learning algorithms.

Initial manual annotations were performed by a single annotator who placed bounding boxes around the structures of interest using a VATIC backend [23] and a self-designed XML administrator web page on the data server desktop. The annotation tool was subsequently changed to CVAT [24] to increase functionality by including segmentation and point annotation with more attributes. Irrespective of the tool used, frames were not annotated where there was significant motion artifact.

Quality Assurance of Annotations

Acquiring the large number of annotations required for machine learning models can be prohibitively slow using a single annotator. In addition, a single annotator may introduce annotation bias. We used a team of 5 annotators in the United Kingdom and India to increase the rate of annotation and to reduce bias, but this posed a new challenge: How can we quantify the acceptable variation between annotators to ensure an achievable standard for the annotation team?

The annotators were sonologists with experience in performing antenatal ultrasound scans. A standard operating procedure was developed (Multimedia Appendix 3), and several metrics were selected to enable comparison between annotators. A standardization exercise was undertaken by the first 2 members of the annotation team, using annotations of 9 recordings of step 1 (6712 frames). These were annotated on a frame-by-frame basis, placing bounding boxes around 11 anatomical features of interest: the fetal head; cerebellum; heart; spine; abdomen; pelvis; stomach and femur; and the maternal bladder, amniotic fluid, and placenta. Following the standardization of the 9 videos, annotators were then assessed on further 20 videos to ensure that their annotations were in line with the standard operating procedure of the annotation. For ongoing quality assurance, every tenth annotation was repeated by a second annotator to ensure consistency was maintained over time.

To guide the expected levels of agreement required for new annotators to achieve and provide an expected standard for ongoing annotation quality assurance, we conducted a baseline intra- and interannotator agreement study. Each of the 2 annotators annotated all the 18,717 frames from 20 videos for the 11 anatomical features described earlier. They repeated all annotations 2 weeks later to allow calculation of both intra- and interannotator agreement.

We developed a code to assess the agreement between sets of annotations available on GitHub [25]. The metrics are calculated as follows:

- Partial match: a frame was denoted as a partial match if >50% of the labels were the same between 2 different annotations.
- Exact match: a frame was denoted as an exact match if the bounding boxes drawn in each frame were the same between 2 different annotations divided by the total number of frames.
- Match per label: closely related to the exact match for an individual anatomical feature, with the denominator as the total number of frames with a given anatomy label by either of the annotators.
- Bounding box intersection over union: calculated for 2 bounding box annotations of the same feature on the same frame. The total area of the bounding box overlap (the intersection) was divided by the area of union between the 2 annotations (total area of both annotators' bounding boxes for any feature minus the area of intersection).

Results

Participants

As of June 2022, a total of 5661 participants have been recruited into the CALOPUS study. After excluding 90 scans following manual quality checking of the scans, 5571 (98.41%) participants remained. Table 1 shows the number of scans acquired at different gestational ages through the iterations of the CALOPUS protocol.

Table 1. Ultrasound data collected as part of the Computer-Assisted Low-Cost Point-of-Care UltraSound (CALOPUS) study.

Gestational age (weeks)	Six-step approach (n=431), n (%)	CALOPUS ultrasound protocol (n=5140), n (%)
<14	4 (0.9)	909 (17.7)
14+0 to 17+6	1 (0.2)	435 (8.5)
18+0 to 24+6	265 (61.5)	1485 (28.9)
25+0 to 29+6	7 (1.6)	354 (6.9)
30+0 to 34+6	69 (16)	1022 (19.9)
≥35+0	85 (19.7)	935 (18.2)

Defining the CALOPUS Protocol

Step 1 of the 6-step approach confirmed presentation in only 60% (46/77) of the cases, whereas step 2 (designed to detect the fetal heart) was able to do so in 99% of the cases (79/80; the single failure was for a twin pregnancy). Conversely, step 2 was able to confirm viability in 81% (62/77) of the videos, and analysis of one or more additional steps was needed to determine fetal heart activity, which was feasible in 99% (79/80) of the participants. Furthermore, steps 3.2 and 5 of the 6-step approach sweep across the same parts of the maternal abdomen, so that a computational algorithm could measure pools of amniotic fluid in step 3.2 rather than requiring a repeat (step 5). Placental location was the most difficult component of the scan to assess. Steps 3 and 4 combined located the placenta in 86% (69/80) of the cases. Ruling out a low-lying placenta was particularly difficult for posterior placentas or those within the lower segment where the cervix could not be visualized.

This initial analysis concluded that a revised protocol for automated decision-making algorithms should be designed to reduce the number of steps owing to redundancy in information obtained. However, more than one step may be needed to achieve each objective, in particular for the determination of placenta location.

We subsequently analyzed 212 scans to assess the impact of step 5 of the CALOPUS ultrasound protocol and bladder filling (Table 2). Our results showed that the cervix was visualized 4-fold more frequently when step 5 of the CALOPUS ultrasound protocol was included as well as step 4 (n=120), compared to 29 times when using step 4 of the CALOPUS ultrasound protocol alone. The bladder was well filled (>200 mL) in 30.7% (65/212) of the women. The cervix was visualized in 91% (59/65) of the cases where the bladder was well filled and both steps 4 and 5 of the CALOPUS ultrasound protocol were assessed, compared with the cervix seen in 28% (18/65) of the scans where only step 4 of the CALOPUS ultrasound protocol was considered. This demonstrates that both bladder fullness and the addition of step 5 of the CALOPUS ultrasound protocol have a considerable impact on the frequency at which the cervix is visualized. The addition of step 5 of the CALOPUS ultrasound protocol is more significant than bladder filling alone.

Table 2. The impact of bladder filling and different steps on visualization of the cervix and classification of placental location.

	Bladder well filled (n=65), n (%)	Bladder poorly filled (n=147), n (%)
Visualization of the cervix		
Step 4 alone		
Seen (n=29, 13.7%)	18 (28)	11 (7)
Unseen (n=183, 86.3%)	47 (72)	136 (93)
Steps 4 and 5		
Seen (n=120, 56.6%)	59 (91)	61 (41)
Unseen (n=92, 43.3%)	6 (9)	86 (59)
Classification of placental location		
Step 4 alone		
Correct (n=165, 77.8%)	53 (82)	112 (76)
Incorrect (n=47, 22.2%)	12 (18)	35 (24)
Steps 4 and 5		
Correct (n=189, 89.2%)	61 (94)	128 (87)
Incorrect (n=23, 10.8%)	4 (6)	19 (13)

It should be noted that it is not always necessary to visualize the cervix to correctly identify whether a placenta is low-lying (eg, when the placenta is at the uterine fundus). Therefore, we examined whether the addition of step 5 of the CALOPUS ultrasound protocol was clinically beneficial by increasing the correct classification of low-lying placental position compared

with a standard ultrasound examination. A protocol including both steps 4 and 5 of the CALOPUS ultrasound protocol correctly classified placentas as low-lying or not in 89% (189/212) of the instances compared to 78% (65/212) with step 4 of the CALOPUS ultrasound protocol alone.

These data indicate that the CALOPUS ultrasound protocol should include a low pelvic brim sweep (step 5). Women should be scanned with a full bladder to optimize visualization of the lower segment and assist in the classification of placental location.

Annotations

Manual annotation is very time-intensive: a video clip lasting 20 to 30 seconds typically takes approximately 40 minutes to fully annotate with bounding boxes. This is because of the time taken to change the size and position of the bounding boxes in response to the probe and fetal movements (despite using an interpolative setting from one frame to the next). The total number of frames recorded for each participant is approximately 4500 (30 frames per second), and so routinely, only 1 or 2 video clips per participant were fully annotated with bounding boxes around the structures of interest, with other videos having frame-level anatomy labels. At the time of publication, 1,541,751 label annotations were made. Overall, 1,026,744 (66.6%) annotations were bounding box annotations around the features of interest, 7788 (0.5%) were segmentations, and 507,219 (32.9%) were labels assigned to frames.

As opposed to bounding box annotation, frame labeling significantly reduces the annotation time but comes at the expense of having no information about the location of a structure within a frame. Table 3 lists the number of videos and frames labeled.

Table 3. Number of video annotations in the Computer-Assisted Low-Cost Point-of-Care UltraSound study.

	Videos (n=1057), n (%)	Frames (n=586,253), n (%)
Step 1	446 (42.2)	254,095 (43.3)
Step 2	161 (15.2)	114,958 (19.6)
Step 3	163 (15.4)	67,633 (11.5)
Step 4	164 (15.5)	103,269 (17.6)
Step 5	123 (11.6)	46,298 (7.9)

Quality Assurance of Annotations

The levels of agreement between annotators and their repeated annotations over 18,717 frames are listed in Table 4. Annotator 2 demonstrated greater reproducibility in annotation than annotator 1, but the same patterns were observed throughout: partial match percentages were higher than for exact label match, and the reproducibility of an annotator's own annotations was greater than the agreement between 2 different annotators. The pooled κ values for match per label demonstrated an excellent level of agreement both between annotators and for repeat annotations, and the bounding box intersection over union >50% was high.

Table 4. Baseline intra- and interannotator agreement in the Computer-Assisted Low-Cost Point-of-Care UltraSound study.

	Intra-annotator agreement		Observed interannotator agreement
	Annotator 1	Annotator 2	
Partial match (%)	98.1	98.3	94.5
Exact match (%)	84	91.1	71.4
Match per label (%)	91.8	95.7	83.1
Pooled κ	0.93	0.96	0.85
Bounding box overlap >50% (%)	94.8	97.1	93.4

Discussion

Principal Findings

The CALOPUS study aims to develop and evaluate simple-to-use clinical protocols and machine learning–based decision-making tools for nonexpert users that are suitable for use in underserved regions. In this paper, we present the methods used to collect clinically relevant, detailed, repeatable, and quality-assessed data for the development of machine learning algorithms for obstetric ultrasound.

Strengths and Limitations

This study has several strengths and uses a multidisciplinary clinical engineering team approach. The prospective nature of data collection allows meticulous quality assurance, which is not possible with retrospective collection of existing clinical data. As a prospective study, it also allows us to collect targeted data for the purpose of machine learning on ultrasound videos, which is not routinely collected in most settings. Preliminary investigation of a machine learning model for automatic detection of breech presentation, built and validated on these data has been described [26], and current work is ongoing to improve this; we are also developing machine learning model

for automatic assessment of low-lying placentas [27] and another for preventing fetal sex determination (mandated in some settings), achieved by automated recognition and obscuring of the fetal pelvic region. We also used a subset of the CALOPUS data and annotations from the Automatic Amniotic Fluid Measurement and Analysis From Ultrasound Video Ultrasound Challenge: Automatic amniotic fluid measurement and analysis from ultrasound videos [28]

We believe that the dual site and international nature of this collaboration increases external validity and enrollment. Nevertheless, this is at the expense of adding complexity to the setup of the study sites and standardization processes. Challenges included training of staff in the use of the ultrasound protocol and annotation of data, which had to be performed remotely. This increased the risk of undesirable changes. Fortnightly meetings between the data acquisition and annotation teams were undertaken to ensure that logistical and technical issues could be identified and corrected promptly and that feedback regarding scanning and annotation variations could be discussed. Despite this, when recruitment speed exceeds annotation speed, problems with data collection may not become evident for some time, as was the case on one occasion. We have now introduced methods to automate some of the quality checks, such as sweep duration to give advice about scanning speed and to identify frames "jumping," which may only be noticed when watching videos at much slower playback speeds.

An important limitation of our study was the use of high-cost ultrasound equipment by expert sonologists. Although our ultimate aim is to develop low-cost ultrasound solutions, there were several reasons why we opted to use a GE Voluson E8 machine during this phase of the study. First, the scan images produced are of high quality. We believe this is a reasonable first step when building machine learning algorithms by training models with high-quality images initially and then introducing lower-quality images later on. Domain adaptation techniques are available for this purpose, which allow parameter refinement from a model built with large data in one domain (in our case, a high-cost ultrasound machine) to a second domain with a small amount of data (in our case, a low-cost ultrasound machine). Second, both clinical sites had GE Voluson E8 machines, which simplified the initiation of the study along with routine clinical scanning. Having demonstrated the feasibility of higher cost systems, we will then translate the models we develop into clinically useful tools to be used by minimally trained personnel with low-cost, handheld ultrasound technology.

Despite being a collaborative project, there have been limitations from the respective ethics committees regarding what data can be shared between sites. Thus, although 1 in 10 scans can be shared for quality assurance purposes, the study design of the machine learning model development and testing was affected. One solution is to build single-site models that use a second site for testing [27]. Another is the use of transfer learning, whereby a model is built at one site and refined using data at the second site. Federated learning is also being considered, where a model is trained on data available at each site separately, and once site-specific models are built, model weights are combined to give a final model [29]. This emerging approach is beneficial as the transfer of original data is not required; rather, encoded weights are shared. We believe this is likely to benefit wider use for multisite machine learning–based imaging research in the future.

Challenges and Further Scope

We observed a lack of universal tools for annotating ultrasound videos. It would be advantageous for there to be open source software that truly caters to the annotation of medical images and videos by accepting multiple file types, enabling measurements to be taken, and allowing frame labeling, bounding box annotation, and segmentation. Currently, several different tools need to be used to perform these tasks.

For most human-executed tasks, reproducibility between ultrasound practitioners is lower than that within the same practitioner [30]. Widely used guidelines exist for the standardized acquisition of ultrasound images in clinical practice [31-33]. We are not aware of any standards for manual annotation and were compelled to develop definitions for labeling different anatomies owing to the complexity of fetal position and movements. The agreement between sonographers assessing a single frame is not 100%, so even a lower agreement is expected when annotating a video consisting of hundreds of frames. The assessment of interannotator agreement is also important in identifying the best level of agreement that could be expected between a human observer and a machine learning model. As manual annotations of anatomical planes provide the only way for the clinical ground truth of anatomical standards to be demarcated, it would be unreasonable to aim for 100% agreement when experienced annotators cannot consistently reach this target of agreement.

Finally, it is worth reflecting on the challenges of interdisciplinary research in this emerging research area. Clinical assessment of CALOPUS videos is novel; therefore, explicitly translating this into a machine learning algorithm input is exploratory in nature. Interdisciplinary research explores the rules needed to assess diagnostic information from both the human and artificial intelligence perspectives. Engineers and clinicians need to work together to understand both perspectives and benefit from regular and clear communication to discuss study design, meet each other's data requirements, and understand differing perspectives about important research questions. Our clinical team has found this an exciting area to work in as it allows a better understanding of clinical decision-making processes when these are explicitly verbalized, whereas the engineering team has found working on real-world clinical problems highly rewarding, as these show interesting, unique challenges not commonly encountered elsewhere.

Conclusions

The CALOPUS study is a unique study that uses obstetric ultrasound videos and annotations from pregnancies dated from 11 weeks and followed up until birth using novel ultrasound and annotation protocols. The data from this study are being used to develop and test several different machine learning algorithms to address key clinical diagnostic questions for obstetric risk management. We also highlight some of the

challenges and potential solutions to interdisciplinary international collaboration.

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Data Availability

The data sets generated and those analyzed during this study are not publicly available owing to ethical constraints. The authors have freely shared a link to assess the agreement between sets of annotations available on GitHub [25].

Authors' Contributions

The project was coled by ATP, SB, and JAN and they are joint senior authors. All authors were major contributors in writing the manuscript, supervised by ATP, SB, and JAN. All authors have read and approved the final manuscript.

Conflicts of Interest

JAN and ATP are Senior Scientific Advisors of Intelligent Ultrasound Ltd but the company has no financial or intellectual property links with the research described in this paper and the described work is entirely based on their academic work.

Multimedia Appendix 1
Members of the Computer-Assisted Low-Cost Point-of-Care UltraSound study group.
[DOCX File , 40 KB - resprot_v11i9e37374_app1.docx]

Multimedia Appendix 2
The Computer-Assisted Low-Cost Point-of-Care UltraSound protocol.
[DOCX File , 17 KB - resprot_v11i9e37374_app2.docx]

Multimedia Appendix 3
The Computer-Assisted Low-Cost Point-of-Care UltraSound annotation protocol.
[DOCX File , 2413 KB - resprot_v11i9e37374_app3.docx]

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Abbreviations

CALOPUS: Computer-Assisted Low-Cost Point-of-Care UltraSound
CRL: crown-rump length
GARBH-Ini: Group for Advanced Research on BirtH outcomes–Department of Biotechnology India Initiative
MVP: maximum vertical pool

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Protocol

Preventing and Protecting Against Internet Research Fraud in Anonymous Web-Based Research: Protocol for the Development and Implementation of an Anonymous Web-Based Data Integrity Plan

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Abstract

Background: Data integrity is a priority in any internet research study; it should be maintained to protect the safety and privacy of human participants and to maintain the validity and reliability of research findings. However, one noteworthy risk of web-based research is fraudulent respondent activity. When investigators must utilize anonymous web-based recruitment techniques to reach hidden and expanded populations, steps should be taken to safeguard the integrity of data collected.

Objective: The purpose of this paper is to present a novel protocol in the form of an anonymous web-based research data integrity plan (DIP) protocol that outlines steps for securing data integrity while conducting anonymous web-based data collection.

Methods: In this paper, we discuss a protocol regarding the development and implementation of a specific DIP in response to fraudulent activity in an original large-scale mixed methods study launched in April 2021. Four primary steps, each with a set of affiliated procedures, are presented: (1) defining the risks, (2) planning research protocols, (3) securing data collection and recruitment, and (4) determining enrollment.

Results: Following the relaunch of a large-scale original study and implementation of the DIP protocol, preliminary analyses demonstrated no fraudulent activity. A pre-post analysis is underway to evaluate the effectiveness of the DIP strategies from February 2022 through May 2023.

Conclusions: Implementing the DIP protocol could save valuable research time, provides a process to examine data critically, and enables the contribution of rigorous findings to various health fields.

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KEYWORDS

data integrity protocol; DIP; anonymous online research; research fraud; IP geolocation; steps and procedures; pre-post intervention outcomes; online; research; protocol; data; privacy; participation; validity; reliability; preliminary; analysis

Introduction

Background

Researchers cannot minimize the importance of data integrity when conducting research. Data integrity is connected to both excellence and quality in research and science for policy [1]. Data are the currency of the digital world and have become necessary for many disciplines to carry out day-to-day activities [2]. The use of technology and electronics worldwide has introduced an array of innovative and instrumental possibilities for scientists and researchers [3]. However, these possibilities have emerging risks. Data integrity risks can directly or indirectly interrupt the recruitment, data collection, data analysis, or interpretation phase of research and ultimately threaten the integrity of outcomes and research findings; if not identified and eliminated, such risks could lead to inappropriate and potential harmful recommendations for practice as well. The threat of hackers or fraudulent data interrupters is most concerning because "altering the grounds of data truth has the potential to destroy prominence (both personally and professionally) and allows intruders to intertwine with cyber security, public health, and safety" (p 854) [2]. The aim of this paper is to introduce an anonymous web-based research data integrity plan (DIP) focused on preventing and protecting against internet research fraud. Moreover, we developed procedures after identifying a data integrity threat in the recruitment phase of a web-based mixed methods research study.

Background on Fraudulent Research Activity

The terms "phishing," farming," and "hacking" are not uncommon concepts in the world of internet technology. However, scientists do not frequently consider fraud in developing survey research. Internet research fraud is becoming a growing concern. Fraudulent users are (1) eligible persons who take a research survey more than once without wrongful intent, (2) eligible persons who repeat a research survey for additional compensation, or (3) ineligible persons who participate in a research survey once or more to benefit from compensation [4].

The use of web-based survey tools and distribution methods (eg, social media) for research can be beneficial for reaching a diverse participant pool but problematic for ensuring data quality. Web-based surveys may be instrumental in reaching stigmatized populations (eg. men who have sex with men) or in seeking information on stigmatized topics (eg, sexual health and drug use) [5-7]; however, there is potential for fraud that could compromise the validity and reliability of data collected from these methods [5-9].

One potential fraud can occur through inattentive responses, which Maniaci and Rogge [9] found to be an issue in their research. While inattentive responses can negatively affect the results of a study, they can also be measured and addressed as part of fraud monitoring [9]. Similarly, attempts at "phishing" can be monitored and managed by researchers as well. In one study, Pozzar et al [7] found that a survey distributed via social media platforms included 100% of fraudulent responses from among the initial ≥270 responses. While troubling, the authors were able to detect the issue, adapt their distribution and screening approaches, and recommend others develop a protocol for monitoring fraud in their research [7]. Ballard et al [5] also emphasized the development of a protocol. They described 3 components that help minimize fraud: "Researchers should have a fraud detection algorithm in place before data collection to ensure that (1) data needed for fraud detection are being collected; (2) the informed consent document can describe that surveys will be evaluated for fraud and what the consequences are for incentives, and (3) fraud can be monitored in real time" (p 9).

Indeed, multiple authors described the data they collected and used to monitor fraud, including geolocation, physical address, email ID, and phone number, among others. For example, Pozzar et al [7] discussed matching the time when a user completed a survey to geolocation data—one of the multiple authors to suggest that geolocation data are best used in connection with other data but not as fraud check alone [5,6]. Bowen et al [6] described using repetitive patterns in usernames, passwords, and email IDs submitted by respondents to register and access incentives because "the promise of even $15 may increase the rate of spurious submissions" (p 9). The requirement of physical mailing addresses for incentives to be sent rather than automatically via email is one way to monitor fraud [5]. Researchers can use physical addresses to match geolocation data. Another potential deterrent is requiring participants to create a unique ID (credential) and log-in information to participate and retrieve incentives [6,10]. Thus, there are many ways in which researchers can help minimize the adverse effects of fraudulent responses.

Defining Geolocation and Geolocation Problems

One way to review and investigate research fraud is through safe and ethically approved use of geolocation. An IP address is one of many components that aid in geolocation; nonetheless, there are numerous issues with how accurate geolocation is [5-7,11]. An IP address, more specifically IP version 4 (IPv4), is a 32-bit address structure that serves 2 primary functions: addressing (the set of rules for networks and hosts to follow to ensure that messages move across the internet efficiently) and fragmentation (essentially breaking down a message into smaller bits of information to transfer across the internet and then putting the data back together in the correct order at its destination) [11]. The next evolution of IP addresses, version 6 (IPv6), accounts for the high demand for IP addresses owing to the ever-increasing use of the internet and the normalization of individuals having multiple devices that connect to the internet [11]. While IPv4 is of 32 bits, IPv6 has 128 bits, allowing for 340 undecillion addresses (or "340 trillion trillion trillion addresses"), creating more than adequate room for continued expansion (p 18) [11].

It is essential to understand the limitations of IP address geolocation [12-14]. First, the accuracy of IP address geolocation varies between IPs. Owing to early adoption and less precise *touchstones* ("reliable network landmarks"), IPv6 is currently less accurate than IPv4 [15,16]. Research innovators who address the network limitations are proposing ways to build the IPv6 network off the IPv4 *touchstones* [16]. Second, country- versus city-level accuracy can vary greatly [13-15]. Many

geolocation databases report 60%-99.99% accuracy at the country level and only 30%-80% accuracy at the city level [17]. Third, the type of network the user is communicating from may impact IP accuracy, with mobile systems reporting far less precision than broadband [14,15,18]. Fourth, and perhaps most importantly, virtual private networks (VPNs) complicate geolocation abilities. A VPN routes a user's IP address through a private network so that the user's internet traffic is encrypted [19]. A user could choose to route their IP through another state and another country entirely.

Methods

Methods Overview

The eligibility survey investigated in this study was reported in accordance with Eysenbach's [20] Checklist for Reporting Results of Internet E-Surveys (CHERRIES) shown in Multimedia Appendix 1 (the CHERRIES Checklist [20] applied to anonymous web-based survey eligibility survey). The preintervention phase with the survey was carried out from April to September 2021 (during original study recruitment), while the postintervention phase was launched in February 2022 (initial study relaunch after DIP initiation) through May 2023.

During the recruitment phase of our study, the research team recognized patterns and suspicious activity that led to the identification of research fraud and data integrity risk. The research methods (anonymous web-based recruitment) and protection of the target population (sexual and gender minority adolescents) made the research more permeable to fraudulent activity. The use of participant compensation for time and web-based anonymous data collection via an electronic survey are common in quantitative, qualitative, and mixed methods research. However, Teitcher et al [4] reported that these elements show an increased potential for Internet research fraud. In the process of (1) integrating specific guidelines for special populations from the Department of Health and Human Services, (2) upholding human subject protection standards for minors outlined in the for the Protection of Human Subjects of Biomedical and Behavioral Research's Belmont Report [21], and (3) offering compensation for study participation, we increased the risk of a data integrity breach. When we determined that research fraud was present and data integrity was at risk, the study was paused to seek institutional review board approval for a newly developed internet research fraud prevention and protection protocol.

The DIP protocol's steps and procedures are outlined in Multimedia Appendix 2 [22-28]. Of note, when engaging with research with web-based recruitment, researchers should be aware of the inherent risks of fraudulent activity. Studies conducted on the internet are not without risk to human subjects. Therefore, researchers should examine and apply principles of *respect for persons*, *beneficence*, and *justice* outlined in the National Commissions for the Protection of Human Subjects of Biomedical and Behavioral Research's Belmont Report [21]. Moreover, the Office for Human Research Protections in the US Department of Health and Human Services outlines special considerations for vulnerable research populations (ie, human fetuses, neonates, pregnant women, children, and prisoners) [29]. These populations require individual assessment for risk and protection, even for internet recruitment and enrollment procedures.

Ethics Approval

This study was approved by the University of North Carolina Wilmington's institutional review board (#20-0126).

Results

As of this writing, a pre-post analysis is in the data collection phase to assess the effectiveness of the DIP strategies outlined in Multimedia Appendix 2 from February 2022 through May 2023. From April 2021 to August 2021, we enrolled 12 participants for semistructured qualitative interviews for a mixed methods study. Before launching the DIP, various indications of fraudulent activity were noted. These include the following: (1) several surveys were entered by respondents but not completed, (2) a rush of survey time stamps was found in the same 1-15–minute period, and (3) exact or similar respondent locations were found among many respondents. The team employed DIP steps 1-3 to secure the survey and then utilized step 4 to review existing data. Researchers determined that 45 unenrolled survey respondents and 3 enrolled respondents were ineligible upon critical analysis of the survey respondent data. Preliminary examination has revealed zero instances of fraudulent activity in the survey from our original study after implementing the DIP in February 2022.

Discussion

The researchers anticipated that implementing the DIP would decrease fraudulent activity in the eligibility survey. This hypothesis remains supported.

Strengths and Limitations

One strength of this study includes the integration of interdisciplinary evidence supporting the development of the DIP protocol. The evidence-based protocol provides future researchers with specific guidance on how to protect their data integrity. When working with vulnerable populations where anonymity is critical, this protocol will enable teams to secure privacy while not jeopardizing the data collection. One limitation is the inability of researchers to control or reasonably estimate the number of participants who may have viewed the recruitment text on the various platforms and not entered the landing page [30,31]. This is one of the inevitable limitations of web-based convenience sampling. To counter this limitation, researchers strategically asked participants who were enrolled and consented to an interview to identify which platform they first learned about the study. This will enable researchers to identify which platforms were most successful for recruitment in future studies.

Future Directions

Overview

Our research team quickly adapted following the experience of research fraud. In addition to the DIP protocol, we offer the following learnings to aid researchers in streamlining efforts

for timely, successful, rigorous, and protected data collection in future studies.

Overcoming Barriers

Research teams may feel defeated when identifying fraudulent attempts to join a study. This deception can be particularly confusing and frustrating when inclusion criteria involve vulnerable populations [5]. Research teams will be optimally prepared if they understand fraud risk in advance, employ methods to uncover these risks, and embrace empathy, even for perpetrators of the fraud. This allows for a quicker team recovery. Harboring feelings of anger and resentment may slow the positive progress of the team's mission. The method of reframing, also referred to as *cognitive restructuring*, is a simple technique to transition from confusion to understanding and empathy [32].

Timely Review

A critical strategy for web-based research recruitment is constant review of incoming data [15,16,27] and smooth communication. Delegation of a DIP protocol is essential for careful review and prevention of research burnout. Research teams should identify who oversees reviewing IP and location issues, how to share that information with the team, who will enact the screening procedures, and how to respond to ineligible participants, owing to the time required to complete fraud prevention strategies [33]. The research team should also consider the benefit of forming a co–principal investigators' (>1 principal investigator) structure to help balance efforts of fraud prevention protocols.

Implications and Conclusions

Medical, health, and other applied science disciplines demand rigorous internet research methods to produce valid and reliable findings. When the results of research are threatened by internet fraud, research budgets are impacted, study timelines are negatively affected, and data lack quality [4]. One essential precursor to conducting rigorous internet medical research is a prevention protocol. Research data integrity involves more than just having a correct data set. Preserving the integrity of research data has critical implications for organizational policy, future development related to health informatics, and the future of internet medical research methods.

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Data Availability

The data sets generated in this study are not publicly available owing to the sensitive nature of the original study and to ensure the protection of the vulnerable population studied.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CHERRIES Checklist [20] Applied to Anonymous Web-Based Eligibility Survey.
[PDF File (Adobe PDF File), 22 KB - resprot_v11i9e38550_app1.pdf]

Multimedia Appendix 2
DIP Protocol's Steps and Procedures to Prevent Web-Based Research Fraud. DIP: anonymous web-based research data integrity protocol.
[PDF File (Adobe PDF File), 125 KB - resprot_v11i9e38550_app2.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
DIP: anonymous web-based research data integrity protocol
IPv4: IP version 4
IPv6: IP version 6
VPN: virtual private network

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Protocol

Success4life Youth Empowerment for Promoting Well-being and Boosting Mental Health: Protocol for an Experimental Study

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Abstract

Background: There is an increasingly alarming worsening of mental health among the youth. There remain significant unmet needs for developing innovative, evidence-based technology–enhanced, positive psychology interventions (PPIs) all-inclusive in targeting psychological distress and risk factors related to high-risk behavior commonly encountered in adolescents.

Objective: We aim to assess the effectiveness of a hybrid (incorporating both synchronous and asynchronous learning) and holistic (targeting social and emotional learning and tackling risk factors unique for this age group) PPI, "success4life youth empowerment," in improving well-being in the youth.

Methods: Students' well-being will be assessed by the 5-item World Health Organization Well-Being Index, and hope will be assessed by the 6-item Children's Hope Scale at week 0, week 8, and week 10, month 6, and month 12. Any improvement in well-being and hope will be measured, estimating the difference in postintervention (week 8 and week 10) and preintervention (week 0) scores by determining the *P* value and effect size using appropriate statistical tests.

Results: This study includes 2 phases: pilot phase 1, delivered by the creators of the succcess4life youth empowerment modules and platform, and phase 2, which will consist of the estimation of scalability through the recruitment of trainers. We hope to start student recruitment by 2022 and aim to complete the results for phase 1 pilot testing by 2023.

Conclusions: We anticipate that a primarily web-based, 10-week holistic PPI can support improvement in the mental wellness of the youth and has the potential for effective scalability.

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KEYWORDS

learned optimism; mind power tool; mental health; success4life, positive psychology-based interventions, well-being; youth empowerment

Introduction

Globally, suicide is the second leading cause of mortality in adolescents and young adults [1]. A cross-national pooled estimate of the suicide mortality rate across all ages, sexes, and countries was found to be 3.77 per 100,000 people in 2019 [2]; however, underestimation and underreporting of youth suicide impact the accuracy of suicide epidemiology [3].

A bidirectional relationship exists between mental disorders and excessive social media use, substance use, and drug dependence, leading to a vicious cycle impacting youth across all communications and countries [4-7]. It has been postulated that even half of the mental and substance use disorders burden

cannot be prevented with current treatments, regardless of the amount of funding available [8]. Data from across the world indicate a further increase in mental health–related emergency visits and reported suicidal ideation and behavior in the youth after the COVID-19 pandemic [1,9-12], despite a decline in screening for suicidal ideation during the pandemic [13]. A study based on a purposive sampling of Google News has revealed that web-based schooling, overwhelming academic distress, and TikTok addiction–related psychological distress are the leading stressors for suicide causalities in the pandemic [9].

The recent action plan on public mental health interventions by the World Psychiatric Association has laid crucial importance on preventing mental disorders and collaboration in delivering these interventions through educational organizations [14]. Primary prevention interventions prevent mental disorders from arising through the promotion of protective factors for mental well-being. Furthermore, as the COVID-19 pandemic fits the definition of a mental health disaster [15], we need innovative and cost-effective universal solutions for enhancing mental wellness that can be exercised at the population level.

Interventions for preventing mental and substance use disorders (MSUDs) during adolescence and early adulthood can be beneficial for promoting community mental well-being as most mental disorders start in this age group [8]. Positive psychology interventions (PPIs) lead to an increase in positive emotions, promote positive functioning, and lead to a reduction in stress and anxiety levels [16,17]. Any positive change in community mental health also leads to overall health, social, and economic benefits through improved productivity, resilience, educational attainment, and reduced risk-taking behavior [18]. PPIs promote well-being among individuals; however, community-level programs based on positive psychology vary greatly in their overall effectiveness [19,20]. Furthermore, the PPIs are typically brief and focus on a single element of positive psychology; for example, gratitude mindfulness, character strengths, or social and emotional skills [21-23]. While some PPIs, such as KidsMatter [24], which operate through improving social and emotional skills, have been particularly helpful for primary schools and early childhood services in Australia, there appears to be a lack of holistic PPIs that not only improve social and emotional skills but also tackle the issues related to social media and drug use for adolescents and young adults. The Hummingbird project [18] in the United Kingdom is an effective universal program for improving adolescent social and emotional skills. Nonetheless, it lacks broader coverage for preventing hazards through social media and awareness of the dangers of drug use. It also lacks a hybrid model incorporating technology-enhanced delivery.

Enthusiasm for technology in mental health–related services has evolved because of its promise to increase the reach of the scalability of services [25,26]. Although technology is regarded as a "new frontier in mental health" [25,27-29], both synchronous and asynchronous learning have pros and cons [30]. Synchronous learning refers to an instructional method wherein the learners interact with the instructor (through the internet or in person) in real time, giving a classroom-like feel. In contrast, asynchronous learning involves interactive learning where the learner and the instructor do not meet at the same time [31]. While synchronous learning permits personal real-time engagement that is more engaging and clarifies misunderstandings and doubts between learners and trainers, the coaching is available for a brief, limited period. On the contrary, asynchronous learning provides more time, a relaxed schedule, and flexibility in accessing educational material.

Technology-enhanced hybrid interventions continue to hold promise for increasing engagement in and enhancing outcomes of evidence-based approaches [25]. We have developed a hybrid PPI "success4life youth empowerment" that adopts unique benefits from real-time synchronous and asynchronous learning and overcomes the individual limitations of each coaching mode. This PPI is also holistic in the spectrum of coverage of elements of positive psychology and targets unique risk factors related to high-risk behavior commonly encountered in this age group. We aim to assess the effectiveness of this PPI in improving well-being and levels of hope in the youth.

Methods

Intervention Course

Earlier, we formulated an evidence-based course curriculum (success4life) for the prevention of MSUDs in the youth [8]. The ultimate objective of the curriculum is the universal prevention (applicable to everyone in the population) of MSUDs in the youth. We have now pioneered the modules, systems, and processes for effectively delivering the success4life program for adolescents and pipeline for emerging adults.

The entire curriculum is designed to provide hands-on coaching on adaptive coping for relieving stress, self-compassion, goal attainment, learned optimism and resilience, and self-protection, including awareness of the dangers of substance abuse and vigilance on social media. Coaching methodology includes hands-on experience in positive psychology with inquiry and project-based, student-directed learning through reflection within real-world experiences and problem-solving. The modules are created using evidence-based, scientific information published in peer-reviewed medical and scientific journals and esteemed books. The bibliography is included after each chapter of the modules. The content incorporated in each module and learners' journal template is protected by intellectual property, granted to Transforming Life LLC, United States (United States copyright office, registration number TXu 2-327-132; approval date July 27, 2022).

Our learning model follows blended digital learning, a combination of synchronous live real-time training and asynchronous e-learning via a learning management system (LMS), providing students expanded access to each week's coaching. Live, real-time training allows sufficient contact with the instructors for effective interactive coaching and learning. The total duration for each weekly session of live training is between 60 and 90 minutes. Live, real-time training can be organized in digital (using videoconferencing technologies) and face-to-face settings. The ideal learner cohort size for group training varies depending on the setting (smaller learner cohort sizes in digital learning environments). During each week's

training, a structured approach is followed for simultaneous project completion. The entire training module is split into 2-4 chapters with journal exercises (assignments) throughout all the chapters. As relevant for some modules, separate project-based learning (PBL) is adopted to enable learners' practical investigations, independence, and reflection within real-world practices. For submission of each week's assignment and course projects, an effective LMS that hosts video modules for asynchronous refresher education and tracks data related to learner's assignment submission, assignment evaluation, and workshop completion certification is used. Students' privacy from the rest of the peers in the group for inquiry-based learning (IBL) through journal completion and submission is critical, and the activity completion is autonomous and independent for each learner. The learners' data privacy will be ensured per local jurisdiction, and the management will collect users' data only for the intended purposes.

The tactical curriculum based on the success4life program (currently marketed by Transforming Life LLC, United States) is designed to impart psychological and mental well-being through adaptive coping for relieving stress, self-compassion, goal attainment, learned optimism and resilience, self-protection, and refraining the vulnerable youth from high-risk behaviors, including addiction to devices, social media, and drug abuse. While other programs aim to enhance well-being in the youth, they neither follow the holistic success4life curriculum nor adopt an integrated framework encompassing the balance of synchronous learning, asynchronous learning, real-time IBL, and PBL. Further details on this concept can be understood using the animation available on YouTube [32].

Modules of the Course

A broad overview of the theme, objectives and chapters is provided below. Module-specific details, including specific IBL and PBL exercises, are illustrated in Multimedia Appendix 1.

Week 1 Workshop: Understanding the Most Complex Yet Extremely Powerful Resource

The overarching objective of this workshop is to give students an awareness and appreciation of our innate potential, which can be harnessed by learning to control and shape our minds and thought processes. Three lessons are included: (1) understanding our mind, (2) the mind-body problem, and (3) the power of our mind.

Week 2 Workshop: Unlocking Your Potential

The overarching objective of this workshop is to provide an understanding of automatic, unconscious thought processes that are generated with little or no awareness and consciousness. The students also learn how to foster a good connection between the conscious and unconscious minds for success and happiness in life. Three lessons are included: (1) understanding our unconscious mind, (2) reprogramming our unconscious mind, and (3) how to apply knowledge in real-life situations.

Week 3 Workshop: Self-transformation

Given all the uncertainties at the current time, we may encounter feelings of hopelessness in our lives. However, each of us can "live an extraordinary life" irrespective of life's challenges. In this workshop, the students learn why and how to expand our consciousness to achieve self-transformation with a deeper fulfillment and purpose. Three lessons are included: (1) what is self-transformation; (2) the relationship between self-transformation and happiness, abundance, and success; and (3) transforming the old self into a new empowered self.

Week 4 Workshop: Building a Sense of Self

The overarching objective of this course is to give students an awareness and understanding of how building self-esteem through self-compassion relates to positive outcomes in life and learn strategies to improve our self-esteem and self-confidence. Three lessons are included: (1) understanding self-image, self-esteem, and self-compassion; (2) building self-esteem and self-confidence through self-compassion; and (3) practicing self-love and self-care.

Week 5 Workshop: Protect Yourself

The overarching objective of this workshop is to give students an awareness and understanding of how our connections through friends, peers, and social media influence our thoughts, choices, and decisions in every way. The impact may be positive or negative, but we are often unaware of this dominance. In this module, students learn to exercise independence in their decisions without peer pressure and resist negative influences. Three lessons are included: (1) conscious connections and due diligence, (2) stay safe: substance abuse awareness, (3) it is okay to say no, and (4) staying vigilant on social media.

Week 6 Workshop: Prioritize, Energize, and Recharge Yourself

In this workshop, the students understand what it is like to practice reflection on their thinking with no or minimal judgment, allowing them to capture each moment with an awareness of change. They also learn to detach from nonbeneficial thoughts such as anger and judgment and let go of unwanted emotions. Three lessons are included: (1) building self-esteem, optimism, and resilience with mindfulness practices; (2) practicing the shield of mindfulness; and (3) meditation exercises.

Week 7 Workshop: Setting and Achieving Goals

In this workshop, the students understand the critical elements related to short- and long-term goals and build on setting personal goals for both the short and long terms. Three lessons are included: (1) discover your passion and purpose, (2) long-term goals, (3) short-term goals, and (4) what stops us from achieving our goals.

Week 8 Workshop: Tactics and Strategies to Achieve Goals in Life

The overarching objective of this workshop is to explain optimism and introduce students to a model to cope with life adversities, teach how to overcome negative thoughts, and convert adversities into opportunities with accurate choices and decisions. Four lessons are included: (1) definition and meanings of "optimism" and "resilience," (2) the ABCDE (Adversity-Beliefs-Consequences-Disputation-Energization) model to cope with life adversities, (3) transforming your

self-talk, and (4) how to turn adversities into opportunities with accurate choices and decisions?

Weeks 9 and 10

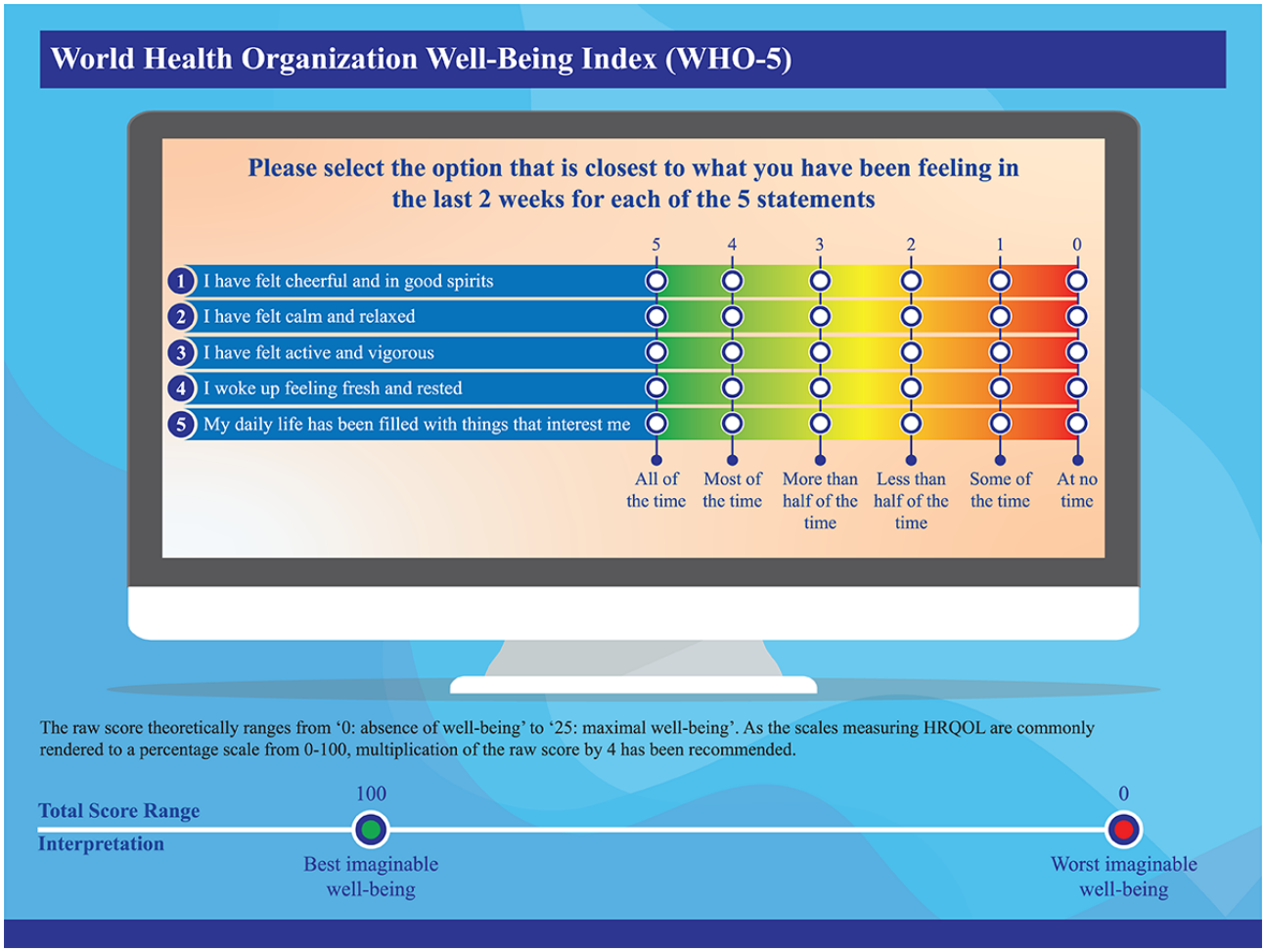
Weeks 9 and 10 include draft and final project presentations by students. Parents are invited to attend the last session. Course completion certifications are awarded for weeks 1-8, upon marking journal assignments completed in the LMS by the instructors. Another reward to the students who complete the entire program successfully includes eligibility into a peer mentor development program.

Study End Points and the Road Map for Their Evaluation

Students' well-being will be assessed longitudinally by the 5-item World Health Organization Well-Being Index (WHO-5) at week 0, week 8, week 10, month 6, and month 12. The WHO-5 well-being index is a short global rating scale that measures subjective well-being for all populations, including adolescents. Positive well-being is another term for mental health (Figure 1) [33]. The key outcome measure includes the positive change in well-being, as estimated by the difference in postintervention (week 8 and week 10) and preintervention (week 0) WHO-5 mean scores by determining the *P* value and effect size using appropriate statistical tests. Although a difference in the mean WHO-5 score of >10 is considered clinically significant [33,34], a meta-analysis of meta-analyses concluded that universal prevention programs of this type in children have effect sizes between 0.07 and 0.16 [35]. Indeed, the difference in the mean WHO-5 score with an antidepressant (desvenlafaxine) vs placebo and wake therapy vs exercise was statistically significant but not clinically significant in patients with depression [36,37].

In children, the hope theory has been introduced on the concept that "goal-directed hopeful thinking" is a requisite for development and survival and is related to experiencing positive emotions [39-41]. Hope within students (≤16 years of age) will also be assessed longitudinally by age-appropriate hope scales at week 0, week 8, week 10, month 6, and month 12. Any improvement in "hope" will be estimated by the difference in postintervention (week 8 and week 10) and preintervention (week 0) mean scores by determining the *P* value and effect size using appropriate statistical tests. Hope theory is related to the theories of learned optimism, self-esteem, and self-efficacy, which are the key goals of the success4life program [42]. Students with "higher hope" have been found to attain higher academic achievement (at all levels of education) and higher graduation rates. They are also better problem-solvers and psychologically adjusted, can handle stress better, are healthier, and have higher self-esteem [43].

Figure 1. Graphical representation for the WHO-5 index. HRQOL: health-related quality of life; WHO-5: 5-item World Health Organization Well-Being Index. Adapted from Topp et al [33]. The WHO-5 well-being index scale is not copyrighted and does not require permission to use [38].



Hope in students aged ≤16 years will be assessed using the Children's Hope Scale (CHS), and the State Hope Scale (SHS) will be used to determine hope for students between 17 and 19 years of age [44]. The CHS measures dispositional hope in children and adopts 6 items on a 6-point Likert scale (Figure 2) [45,46]. The SHS is also a brief 6-item scale. However, responses are rated on an 8-point Likert scale (Figure 3) [47-49].

Figure 2. Graphical representation of the Children's Hope Scale. Adapted from Snyder et al [46]. The Children's Hope Scale is not copyrighted and does not require permission to use [44,45].

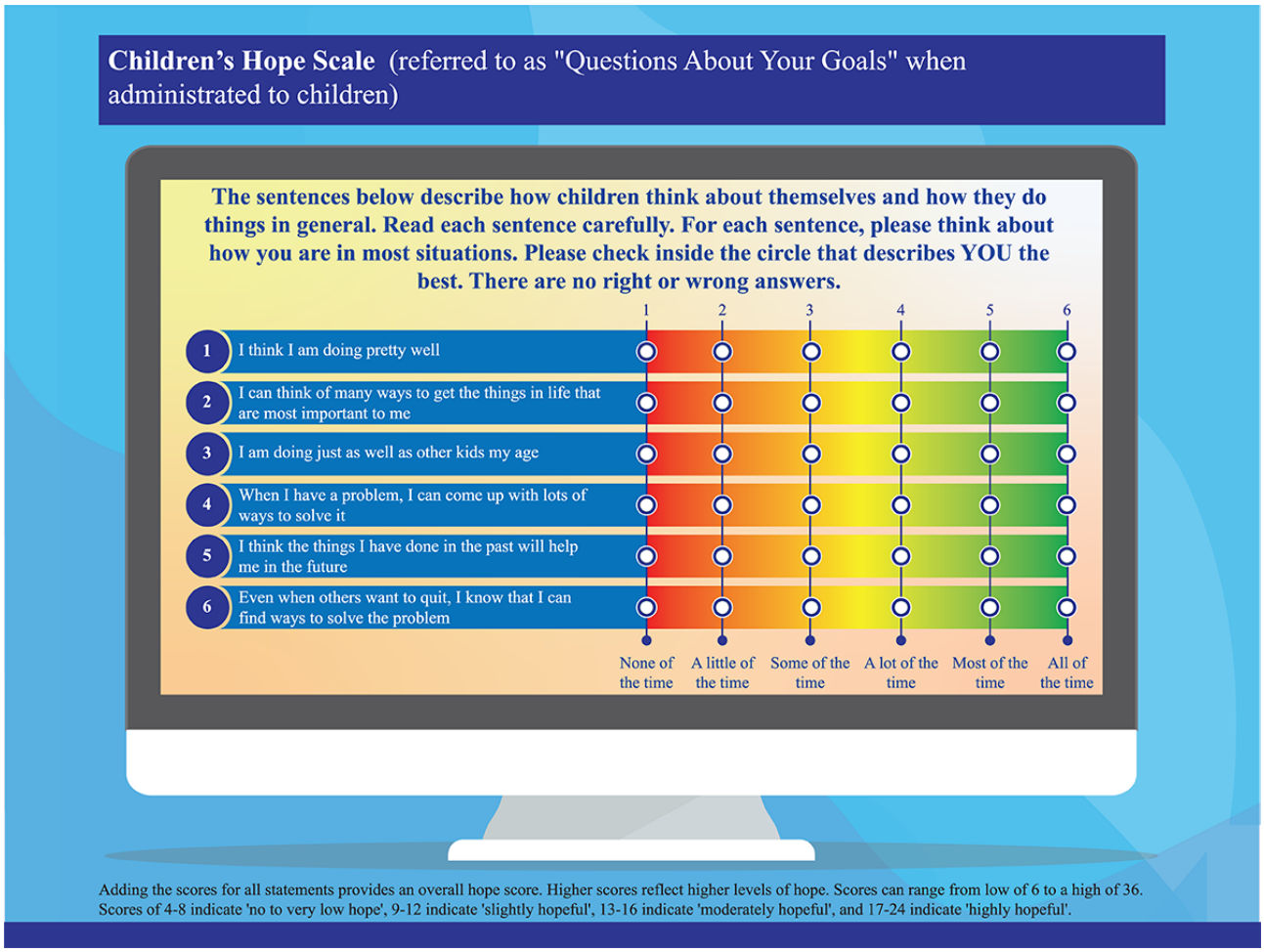


Figure 3. Graphical representation for the State Hope Scale. Adapted from Snyder et al [46,49]. The State Hope Scale is not copyrighted and does not require permission to use [44,50].

There are separate WHO-5 and hope surveys at weeks 8 and 10 to analyze the effect of PBL, which will be covered mainly in the last 2 weeks. All the scales (WHO-5, CHS, and SHS) have been validated, are not copyrighted, and as such do not require permission to use [38,45,50]. Figures 1, 2, and 3 provide a graphical representation of the WHO-5, SHS, and CHS, respectively

At the end of each workshop in weeks 1-8, the students will also rate the effectiveness of each training session (as the usefulness of training in day-to-day life and ability of the movement in achieving its objectives), report a net promoter score as a metric to study learner satisfaction, and evaluate the performance of the trainer using a brief anonymous closed-ended postworkshop web-based questionnaire. Descriptive statistics will compare the students' aggregate responses for each week.

Surveys will be conducted in accordance with the global standards of good clinical practice (as defined by the International Conference on Harmonization E6 Guidelines for Good Clinical Practice) [51], the latest version of the Declaration of Helsinki, and the national regulations [52].

Ethics Considerations

At week 0, interested participants' legal guardians will complete the "enrolment agreement form" as part of the onboarding process for parents and guardians. Informed consent will be obtained from the legal guardians of students. The program's effectiveness will be assessed by a series of web-based questionnaires conducted on recruited students whose parents or guardians provided informed consent for the study. All the research questionnaires directed to the students are entirely anonymous, voluntary, and close-ended.

The research methodology is exempt from the requirement of ethics committee approval according to the Office for Human Research Protections, US Department of Health and Human Services, as the survey questionnaires will be completely deidentified [53,54]. Any suspected cases of justifiable concerns related to physical or mental health will be brought to the attention of relevant responsible party (eg, school counselors, parents, or legal guardians).

Results

The study has 2 phases. A pilot phase (phase 1) will involve the recruitment of approximately 100 adolescent students between the ages of 13 and 19 years from the United States. Coaching will be preferably digitally and mainly conducted by the creators of the modules (2 physicians and a psychology educator with a doctorate). Phase 2 will involve training the trainers program. The "new coaches" could be teachers and peer mentors (with nonscientific backgrounds) or psychology, medical, or science graduates and postgraduate students who

will contribute to making a larger social impact once the program is fit to scale. The target number of participants in phase 2 will be between 500 and 1000. Results from phase 1 will serve as an external control to test the effectiveness of the scalability platforms. The sample size predictions for phases 1 and 2 are based on a similar PPI, the Hummingbird Project from the United Kingdom, which led to improvements in adolescents' well-being, also measured using the WHO-5 [18]. We anticipate to start student recruitment by 2022 through partnering with schools, family, and youth organizations and aim to obtain the results of phase 1 pilot testing by 2023.

Overall, we expect to see positive effects on students' well-being and to enhance competency for essential life skills, including coping with adversities through learned optimism, decision-making, problem-solving, resisting peer and social media influences, and self-control through our success4life program.

Discussion

The scientific breakthroughs through effective vaccinations and medications have helped prevent severe COVID-19 infection and deaths [55,56]; however, much of the work remains unfinished until we effectively tackle the rising mental disorders in the youth [57]. The challenge is to continue to direct innovation and science to effectively "flatten the curve" of increasingly alarming psychological distress in the youth, especially adolescents [15,58].

In this paper, we describe a holistic program developed by our team aimed to tackle the key challenges faced by adolescents in the modern age with technology-enhanced, real-time, hands-on experience on positive psychology. Our program uses IBL and PBL techniques to provide teenagers and emerging adults with methods for adaptive coping for relieving stress, self-compassion, goal attainment, learned optimism and resilience, and self-protection. In addition, we include modules on the awareness of the dangers of substance use and vigilance on social media. To our knowledge, this is the first time such a program has been developed, and we propose here a method to test its effectiveness and scalability.

Real-world data (RWD) consist of information collected during routine clinical, counseling, or coaching practice [59-61]. Real-world evidence (RWE) originates from studies based on valid RWD collected outside traditional controlled clinical trial programs. RWD, however, involves inherent biases and must be fit for the purpose of generating RWE. Challenges of RWD include data quality, reproducibility, replicability, and accuracy, which may affect validity [59].

The research methodology for the generation of RWD includes implementation science, qualitative research, translational research, participatory research, surveys, precision medicine, and mixed methods research [60]. Deidentified anonymous data enable researchers to study the effectiveness of mental health interventions, treatment, and services by observing outcomes recorded within routine sessions [61].

Two serious concerns with RWD include reproducibility and replicability [62]. Ideally, a study testing an intervention should be reproducible through not only direct replication (adopting the same methodology) but also conceptual replication (adopting a different methodology) [63]. For a universal PPI to have a viable future and make a public impact, it needs to be scaled up and delivered by multiple trainers on multiple sites [18]. Our main research will check the effectiveness of the same intervention (success4life program) upon scaling through the *train the trainer* program for conceptual replication of the intervention. Minor amendments in the intervention to fix any inefficiencies or flaws, as evidenced by pilot testing, are permitted and will be documented.

Students are generally reluctant to answer IBL questions about their own experiences or opinions, not only owing to fears about revealing personal information to peers but also because they are often afraid that they may give "wrong" answers [64-66]. To overcome this hesitancy, all IBL journal completions for our intervention are real-time, digital, technology-based submissions through an LMS that protects the student's anonymity and privacy to peers. A clear statement that there are no right or wrong answers will be implemented in all journals during each workshop. The PPIs designed to improve well-being are often compared to waitlist controls, which leaves ambiguity and unmeasured confounders related to their effectiveness [67]. Hence, we will not have any separate control group and will only study the change from baseline.

Randomized controlled trials (RCTs) with homogeneous study populations and double-blind study designs with statistical sample size and study calculations before the start of the study are the gold standard for determining the efficacy of interventions [68]. Our study lacks an RCT study design and a statistical sample size calculation, which could introduce bias. We decided to adopt an RWD design because RCTs on universal social and emotional learning programs have shown controversial findings [69], as often digital interventions show meaningful improvements only when tested under strictly controlled research settings [70]. Furthermore, although RCTs carry a high internal validity, the external validity or generalizability of the results to a wider population is always a concern with RCTs owing to strict inclusion and exclusion criteria [68,71].

Nonetheless, real-world studies on heterogeneous populations without randomization are subject to bias and confounders [71]. The scientific best practices roadmap we adopted for scientific strategies needed to draw valid causal conclusions on the effectiveness of the success4life program includes the adoption of robust and validated study end points and publishing of the study protocol to enhance study transparency. We also use neutral instead of negatively or positively phrased items and measures to avoid central tendency bias (in Likert scales) for the weekly workshop feedback questionnaires, using closed questions in the survey. We decided to make the response to all questions mandatory for submission of each feedback questionnaire to avoid any issues of missing values in data sets and to keep the surveys fully anonymous yet voluntary to prevent nonresponse bias [59,63,72,73].

Pessimistic explanatory style (self-talk and the way people explain to themselves why they experience bad or good events)

leads to cognitive vulnerability to depression, poor health, and early mortality [74,75]. Many factors—for example, the explanatory style of parents (especially that of mothers) for their and their children's events along with childhood trauma, chronic adversity, and abuse—influence the development of a pessimistic explanatory style as a trait [74-76]. Interventions aimed at changing a pessimistic explanatory style and outlook enhance mental and physical well-being and lower the likelihood of future illnesses [76,77]. This is also relevant for breaking the cycles of intergenerational trauma and ever-increasing psychological distress in the youth by promoting protective processes that not only buffer against life's uncertainties but also intergenerational risk and provide immunization against mental health disorders [78,79].

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Data Availability

Multimedia Appendix 1 contains a PDF document entailing an infographic-based broad overview of the theme, module-specific complete details, and research phases of the study.

Authors' Contributions

All the authors are involved in conceiving the research idea and design. Dr Sajita Setia was involved in manuscript writing, and all authors were engaged in revising it for scientific content and approval before its submission for publication. All the authors have also read and approved the final version.

Conflicts of Interest

The authors are the creators of the success4life youth empowerment program and are the shareholders of a start-up, Transforming Life LLC.

Multimedia Appendix 1
Broad overview of each workshop's specific details, including the theme, objectives, and specific IBL and PBL exercises. IBL: inquiry-based learning. PBL: project-based learning.
[PDF File (Adobe PDF File), 3563 KB - resprot_v11i9e38463_app1.pdf]

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Abbreviations

ABCDE: Adversity-Beliefs-Consequences-Disputation-Energization
CHS: Children's Hope Scale
IBL: inquiry-based learning
LMS: learning management system
MSUD: mental and substance use disorder
PBL: project-based learning
PPI: positive psychology intervention
RCT: randomized controlled trial
RWD: real-world data
RWE: real-world evidence
SHS: State Hope Scale
WHO-5: 5-item World Health Organization Well-Being Index

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Protocol

Individualizing the Oncological Treatment of Patients With Metastatic Non–Clear Cell Renal Cell Carcinoma by Using Gene Sequencing and Patient-Reported Outcomes: Protocol for the INDIGO Study

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Abstract

Background: No phase 3 studies have yet been conducted for patients with non–clear cell (CC) renal cell carcinoma (RCC) exclusively due to the rare occurrence of the disease and the heterogenicity in tumor morphology. Consequently, there is no evidence of the optimal treatment, and new approaches are needed. One approach is individualizing treatment based on the gene sequencing of tumor tissue. Additionally, recent studies involving the patient-reported outcomes (PROs) of patients treated for metastatic cancer have shown significant benefits for quality of life, median overall survival, and overall survival. The use of gene sequencing and PROs can be of great importance to patients with rare cancer types, including patients with non-CC RCC, and should be investigated in clinical trials, especially for cases where evidence based on phase 3 studies is difficult to obtain.

Objective: We describe the INDIGO study, in which patients, based on gene analyses, will be allocated into 4 treatment arms containing 14 treatments and use electronic PROs. We aim to improve the treatment of patients with non-CC RCC. The end points in the study will be the overall response rate (complete and partial) in the total patient population, which will be based on the RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria, and the time to treatment failure.

Methods: INDIGO is a prospective phase 2 trial, and 30 patients will be enrolled. The patients will receive systemic treatment based on genetic analyses of their tumor tissue. All patients will receive electronic questionnaires in a dedicated app—a questionnaire regarding symptoms and side effects and another regarding health-related quality of life. Depending on the treatment regimen, the patients will be seen by a medical doctor every third, fourth, or sixth week, and the effect of the systemic treatment will be evaluated every 6 weeks via a computed tomography scan. The study has been approved by the Danish Medicines Agency and the National Committee on Health Research Ethics (approval number: H-19041833), complies with good clinical practice guidelines, follows the General Data Protection Regulation, and is registered at the Capital Region of Denmark.

Results: Recruitment started in March 2020, and at the time of submitting this paper (June 2022), a total of 9 patients have been enrolled.

Conclusions: We aim to explore methods for improving the treatment outcomes of patients with non-CC RCC, and the INDIGO study will contribute further data on personalized medicine for rare types of RCC and provide new knowledge on the active use of electronic PROs.

Trial Registration: ClinicalTrials.gov NCT04644432, https://clinicaltrials.gov/ct2/show/NCT04644432 ; European Union Drug Regulating Authorities Clinical Trials Database 2019-001316-38, https://tinyurl.com/2p8mb4aw

International Registered Report Identifier (IRRID): DERR1-10.2196/36632

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KEYWORDS

patient-reported outcome; electronic patient-reported outcome; renal cell carcinoma; non–clear cell renal cell carcinoma; health-related quality of life; oncology; targeted therapy; precision medicine; eHealth; outcome; patient-reported

Introduction

Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for about 80% of all renal tumors, and the age of onset is typically 60 to 70 years. The majority of patients have clear cell (CC) histology, but 20% have another histology, and this group is referred to as *patients with non-CC RCC* [1]. CC histology is mostly characterized by a von Hippel-Lindau gene defect, whereas non-CC histology comprises different subtypes that each have individual morphological and genetic characteristics [2].

There is no evidence of the optimum treatment of non-CC RCC. No phase 3 studies have been conducted for patients with non-CC RCC exclusively (ie, not for the individual subtype or for the whole group). Data are available from subgroup analyses and the expanded access programs of large studies [1,3-5]. Generally, patients with non-CC RCC have poorer prognoses than those of patients with CC RCC, with an overall survival of 12.8 versus 22.3 months and a time to treatment failure (TTF) of 4.2 versus 7.8 months [2]. The overall response rate (ORR) has been reported in the range of 10% to 27% for patients with non-CC RCC, whereas an ORR of up to 71% has been reported for patients with CC RCC [2,6-11].

Use of Patient-Reported Outcomes

Throughout several decades, patients' symptoms and side effects have been assessed by clinicians during consultations. A lexicon—the Common Terminology Criteria for Adverse Events (CTCAE)—that is used to report and grade adverse events was developed in relation to pharmaceutical development, and it is used by clinicians in both clinical trials and daily routines. To date, the CTCAE is the foundation of symptom scoring for patients during active oncological treatment [12]. Nonetheless, research shows a discrepancy between symptoms scored by patients and clinicians where clinicians underscore the severity of the patients' symptoms [13,14]. Safety and toxicity reports are crucial in clinical trials and must be reliable, making this discrepancy problematic. Since 2009, the incorporation of patient-reported outcomes (PROs) in pharmaceutical research has been a part of guidelines and recommendations [15]. Although the collection of PRO data has taken place for decades, often in terms of quality of life data from patients participating in clinical trials, these data were not being used during data collection, and the focus became benefitting populations of patients instead of directly benefitting the individuals who shared such information. This is called the *passive use of PROs*.

The active use of PROs is now being implemented to a larger extent, and data are being used in real time to give feedback to patients. Recent studies involving the active use of the PROs of patients treated for metastatic cancer have shown significant benefits for health-related quality of life (HRQoL), median overall survival, and overall survival [16,17]. The use of PROs as end points in clinical studies can be of great importance to patients with rare cancer types, including patients with non-CC RCC, for whom treatment is highly individualized, and evidence based on phase 3 studies is difficult to obtain. This approach allows for the individualization of care for each individual patient. Such information strengthens clinical decision-making, as it can be used for detecting changes in a patient's condition that would otherwise be overlooked or reported later.

The National Cancer Institute created the PROs Version of the CTCAE (PRO-CTCAE), which includes adverse events that are appropriate for self-reporting [18]. In 2016, the PRO-CTCAE was translated into Danish and validated by Baeksted et al [19].

Gene Analysis

In the IMmotion150 study [20], it was shown that patients can be divided into groups with either an angiogenic or immune profile, depending on the RNA expression of relevant genes. The study showed that giving patients with a certain profile a treatment that targets the profile had a positive effect on progression-free survival (PFS). These findings have since been validated in the IMmotion151 study [21].

At present day, Danish patients with metastatic non-CC RCC who are fit to receive systemic oncological treatment are offered tivozanib, regardless of their histological subtype, unless the patients have a sarcomatoid component or collecting duct RCC.

The possibilities for individualizing treatment are increasing, as results of gene analyses can be made available within a few weeks via next-generation sequencing. Instead of treating patients with non-CC RCC as 1 homogeneous group, the INDIGO study will investigate whether patients' future course of treatment can be individualized based on knowledge about the gene alterations in their tumor tissue and via the active use of PROs.

Hypothesis

Our hypothesis is that basing the choice of first-line treatment on the DNA mutations in and RNA profiles of a heterogeneous patient population will increase the ORR of the total population to 30% (10% has been reported for historical cohorts). To achieve this goal for patients with non-CC RCC, we will give

personalized medicine and use electronic PROs (ePROs) actively.

Methods

Recruitment

Patients with non-CC RCC or 100% sarcomatoid RCC who have been referred to the Department of Oncology at Copenhagen University Hospital – Herlev and Gentofte to receive first-line systemic treatment for metastatic disease can participate in the study if the inclusion and exclusion criteria are met. Patients from other centers in Denmark will be offered referral to the department for the purpose of participation in the INDIGO study.

The inclusion and exclusion criteria were chosen to mimic the inclusion and exclusion criteria for research on RCC in general. These can be seen in Textbox 1.

Textbox 1. Inclusion and exclusion criteria. CC: clear cell; RCC: renal cell carcinoma.

Inclusion criteria

- Signed informed consent
- The patient must be willing and able to follow the protocol
- Age of ≥18 years
- Inoperable, locally advanced, or metastatic disease with non-CC RCC found to be unsuited for surgery with a curative intent
- Sufficient tissue for DNA analyses (corresponding to 10 slides) and RNA analyses (corresponding to 1000 tumor cells).
- Measurable disease according to the RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria
- Women must have a negative pregnancy test, not be breastfeeding, or be of nonchildbearing potential (menopausal, hysterectomy, or ovariectomy)
- Women of childbearing potential (<2 years after last menstrual period) and men must use effective contraception (pills, intrauterine device, diaphragm, or condom with spermicide or sterilization) or be sexually abstinent during the treatment with the experiment medicine and up to 7 months after the discontinuation of the medicine
- Karnofsky performance status of ≥70%
- Life expectancy longer than 3 months
- Baseline blood samples for hematology
  - Leucocytes: ≥3.0 × 109/L; platelets: ≥100 × 109/L; hemoglobin: ≥6.2 mmol/L
- Biochemistry:
  - International normalized ratio of ≤1.5
  - Activated partial thromboplastin clotting time of ≤1.5 times the upper limit of normal
  - Total bilirubin of ≤1.5 times the upper limit of normal
  - Aspartate transaminase and alanine aminotransferase of ≤2.5 times the upper limit of normal for patients without liver metastases and ≤5 times the upper limit of normal for patients with liver metastases
  - Estimated glomerular filtration rate of >30 mL/min

Exclusion criteria

- Prior systemic treatment for metastatic renal cell carcinoma
- Prior adjuvant treatment with immune-checkpoint inhibitors
- Major surgical procedure, open surgical biopsy, or significant trauma within 28 days prior to treatment initiation
- Serious nonhealing wound, ulcer, or bone fracture
- Autoimmune disease or other condition requiring systemic treatment with either corticosteroids (>10 mg/day of prednisolone or similar) or other immunosuppressive drugs
- Metastases in the central nervous system; the patient must undergo a magnetic resonance imaging scan (preferred) or computed tomography scan of the brain within 28 prior to treatment initiation
- Seizures that cannot be managed with standard medical treatment
- If urine dipstick indicates ≥3+ protein, urine must be collected over a period of 24 hours (must be <3.5 g/day of protein), and if dipstick indicates degree 2 proteinuria, urine must be collected over a period of 24 hours prior to each prescription
- Other malignancy within 5 years (except for curatively treated basal cell carcinoma of the skin and/or cervix carcinoma in situ)
- Uncontrolled hypertension (≥150 mm Hg for systolic blood pressure and/or ≥100 mm Hg for diastolic pressure) despite maximum antihypertensive medical treatment.
- Treatment using other investigational drugs or participation in other studies
- Clinically significant (ie, active) cardiovascular disease, such as cerebrovascular conditions (≤6 months), myocardial infarction (≤6 months), unstable angina, New York Heart Association congestive heart failure (degree 3 or greater), or serious cardiac arrhythmia requiring medical treatment; patients with well-managed atrial fibrillation/atrial flutter may be included
- Previous or current other diseases, metabolic dysfunction, clinical findings on physical examination or clinical laboratory findings that give suspicion of a disease or condition that would contraindicate the use of an investigational drug, or a patient with a high risk of treatment complications
- Patient cases where the investigator finds that patient compliance prevents the safe completion of the treatment

Design

Our study is a prospective, 4-arm, single-center, phase 2 trial at Copenhagen University Hospital – Herlev and Gentofte, Denmark.

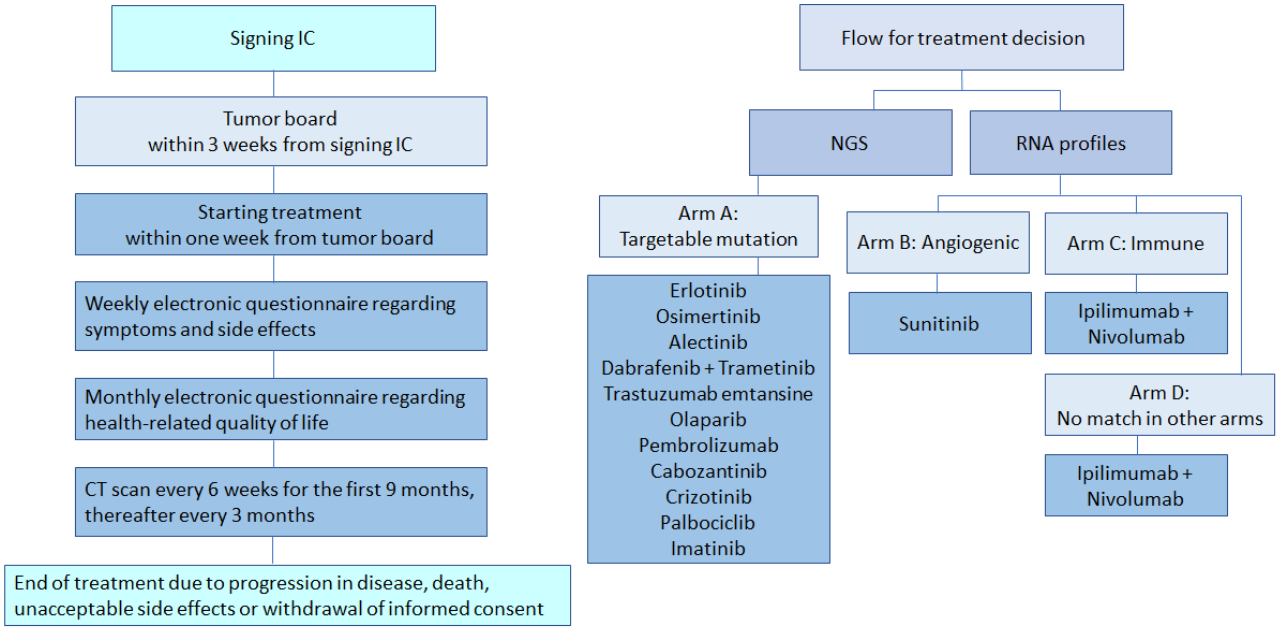
Each enrolled patient will receive oncological treatment based on the results of the genetic analyses of tumor tissue. Next-generation sequencing analyses will be performed with the FoundationOne CDx assay from Foundation Medicine, Inc. The tumor tissue undergo hybridization capture-based targeted sequencing for 324 cancer-related genes; gene alterations; and rearrangements, including microsatellite instability and tumor mutational burden. The RNA analyses will be performed at the hospital's Department of Pathology to search for an immunogenic or angiogenic RNA profile [20].

The results of the RNA and DNA analyses will be discussed by a multidisciplinary tumor board, which decides on the treatment offered to a patient. Patients can be allocated to 4 different treatment arms that represent the flow used to allocate the patients. The study flow and treatment arms are shown in Figure 1. If a patient fits into more than 1 arm, the patient will be assigned to the arm that is closest to the first treatment arm—arm A. It is important to emphasize that the design of the study is not to compare the different treatments. The first treatment arm—arm A—is for patients with a targetable mutation, arm B is for patients with an angiogenic profile, arm C is for patients with an immune profile, and arm D is for patients that do not fit into any of the other treatment arms.

Depending on treatment regimen, patients will be seen by a medical doctor every third, fourth, or sixth week to receive treatment. Additionally, the effect of the systemic treatment will be evaluated every sixth week via a computed tomography scan. The patients will receive treatment until clinical or radiological progression, until the patients experience unacceptable toxicity, or until they withdraw their consent to participate in the study.

The intervention in the trial is treatment according to a gene profile combined with the active use of ePROs. Independent of the treatment regimen, the patients will receive 2 electronic questionnaires regarding symptoms, side effects, and HRQoL. At every consultation, the patients' side effects and symptoms will be discussed and graded by a clinician in accordance with the CTCAE, and a physical examination will be performed.

Figure 1. INDIGO study design and flow. CT: computed tomography; IC: informed consent; NGS: next-generation sequencing; RNA: Ribonucleic Acid.



The ePROs

All patients will complete a weekly questionnaire consisting of 32 questions regarding 17 symptoms and side effects, which were chosen from the PRO-CTCAE library. The different symptoms are shown in Textbox 2. Regardless of their treatment, the patients will answer the same questionnaires, which use the same advice algorithm. The questions were selected by a group of experts consisting of 4 experts in the oncological treatment of kidney cancer and 2 experts in PROs. The questions were chosen based on the expected frequencies of the symptoms and side effects in all 4 treatment arms and their possible treatments. Rare but potential critical symptoms were also chosen (eg, hemoptysis). The questions were chosen from the validated PRO-CTCAE library and the validated Danish translation of this library.

The questionnaires will be completed in an app, and the patients will immediately receive advice based on their responses. The advice (ie, predefined symptom-handling advice) will be given after an algorithm which is decided on by the expert group. The advice will depend on the severity of the symptoms or side effects reported, and the thresholds for different advice will be decided individually for each question, depending on the symptoms. The questionnaires and advice are in Danish.

The European Organization of Research in Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) will be completed by the patients every 4 weeks from the start of

treatment until the end of treatment. The 4-week schedule was chosen as a compromise among the different treatment regimens (3-, 4-, and 6-week schedule) and due to the possible short participation in the study. The collection of HRQoL questionnaires is an example of the passive use of PROs.

Health care professionals will assess the incoming responses from the patients daily and can contact the patients if necessary. The health care professionals will not receive an alert when a patient has answered a questionnaire, but patients with the most severe symptoms will appear at the top of the list in the clinician interface. At consultation, the PRO responses will be used as a tool and starting point for conversations between the clinicians and patients.

The interfaces for both patients (Figure 2) and clinicians (Figure 3) were specifically developed for the INDIGO study. The questionnaires will be sent to the patients via an app from Journl. Journl is an app provider that specializes in PROs and is International Organization for Standardization (ISO) 13485 and ISO 27001 certified. Before the first treatment, the patients will be instructed to download the app on their smartphones; create a user profile; and complete the first two questionnaires, which represent the baseline. The patients will log onto the app with a personal ID number code. If a patient has uncompleted questionnaires, they will receive daily telephone notifications until the questionnaires are completed. At the end of treatment, the patients will receive a patient-reported experience measure questionnaire in Danish for evaluating patients' satisfaction with the ePROs [22]. In this questionnaire, the patients will assess, among other things, the length of the questionnaires, whether the questions were understandable, and whether they believed that the questionnaires had a positive influence on their communications with the health care professionals.

Textbox 2. Symptoms in the electronic patient-reported outcomes questionnaire.

Symptoms

- Decreased appetite
- Nausea
- Vomiting
- Diarrhea
- Dyspnea
- Cough
- Pain
- Oral mucositis
- Hypertension
- Fatigue
- Headache
- Dizziness
- Rash
- Pruritus
- Sore muscles
- Coughing blood
- Blood in stool

Figure 2. Patient interface in the Journl app. Text has been translated to English.

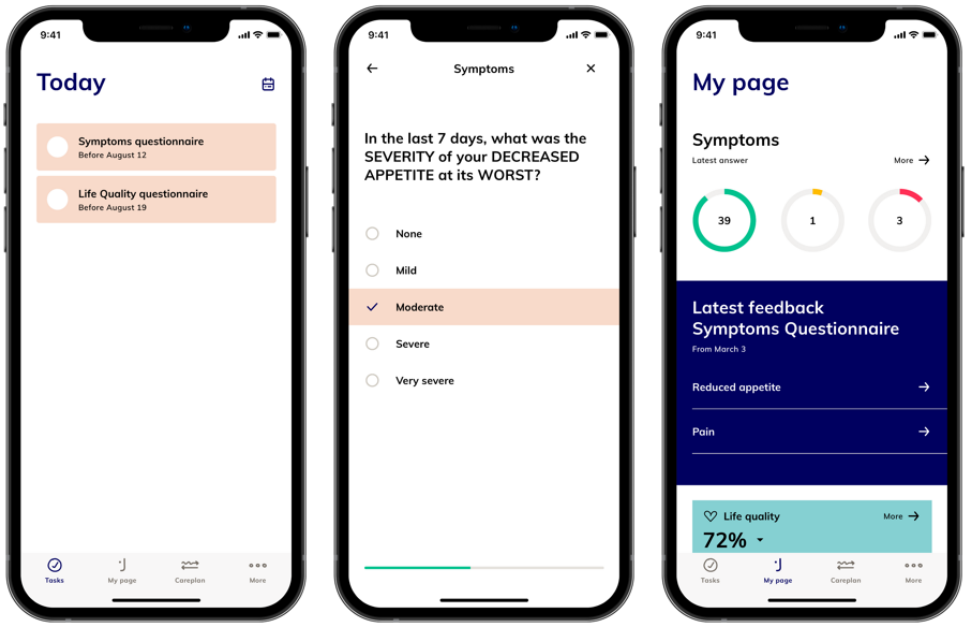
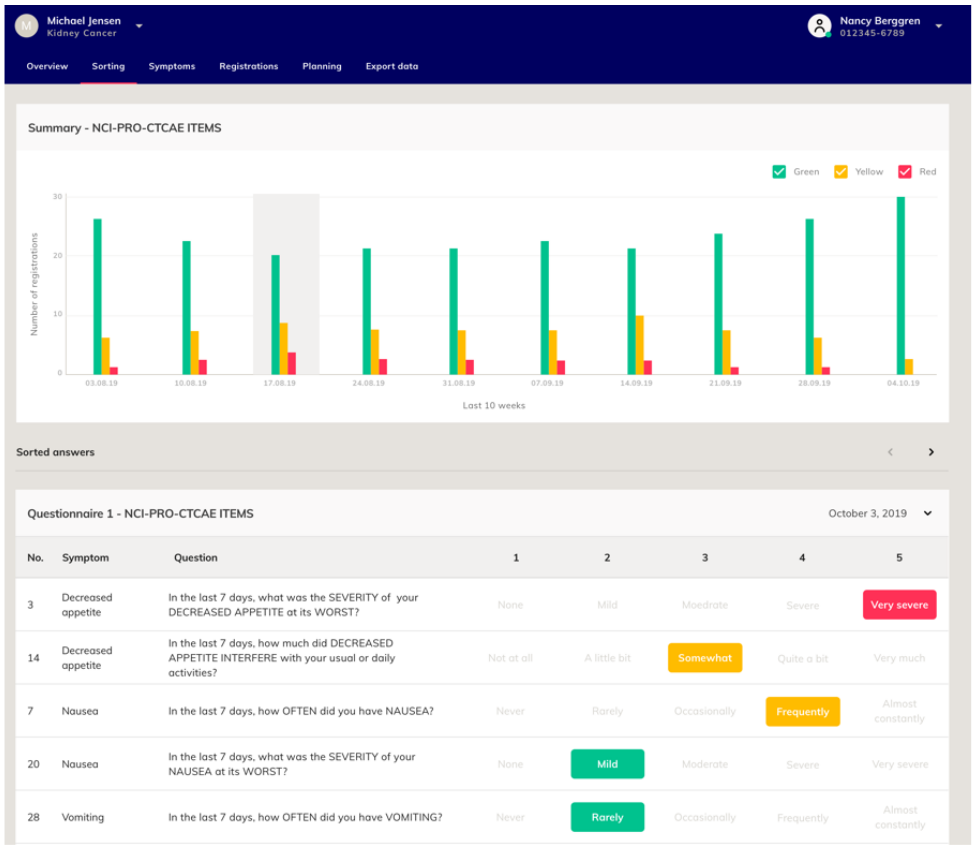


Figure 3. Clinician interface in the Journl web application. Text has been translated to English.



End Points

The INDIGO study is a study in which new workflows, including testing new treatment options based on DNA mutations and RNA profiles, and the ePROs of patients with non-CC RCC will be used. The two primary end points are the ORR (complete and partial) in the total patient population, which will be based on the RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria, and the TTF. The RECIST version 1.1 criteria are standards for evaluating treatment response by measuring changes in the size of tumor tissue. Computed tomography is the preferred modality, and 2 or more target lesions will be chosen at baseline. Afterward, the lesions will be assessed on an ongoing basis. The following secondary end points will be measured: the use of PRO tools during treatment in terms of the completion of weekly questionnaires, in terms of possible patterns in the completion of questionnaires, and in terms of following the instructions regarding contacting the hospital if a patient receives advice to do so. The HRQoL

questionnaire (ie, the EORTC QLQ-C30) responses will be converted to values in a graph. Changes in quality of life will be compared with the completion of the patients' PRO questionnaires. The patients will evaluate their satisfaction with the use of PROs on the validated Patient Feedback Form [22].

Other secondary end points are PFS, overall survival, the disease control rate (ie, complete response, partial response, and stable disease based on the RECIST version 1.1 criteria), the duration of responses, the number of hospital admissions, and the number of adverse events (ie, those in the CTCAE).

Statistical Analysis

The data will be analyzed with the statistical software R Statistics (R Foundation for Statistical Computing).

Descriptive statistics will be used to describe symptom patterns based on PROs. Further analysis of covariance and 1-tailed *t* tests will be used to estimate changes in selected symptoms and HRQoL from baseline.

Descriptive statistics will also be used to describe patient characteristics and estimate the clinical end points—the ORR, PFS, the TTF, overall survival, the disease control rate, and response duration. PFS, the TTF, overall survival, and response duration will be calculated by using the Kaplan-Meier method. Patients who are alive or have emigrated will be assessed at the end of the follow-up.

Univariate and multivariate analyses will be carried out to assess prognostic factors, based on a Cox proportional hazard regression with 95% CIs. Differences in baseline characteristics will be calculated by using the chi-square test. The case-deletion method will be used in cases of missing laboratory samples, and if possible, multiple imputation will be used.

Power

When the INDIGO protocol was drafted, the ORR was reported in the range of 10% to 16% for patients with non-CC RCC, whereas an ORR of almost 28% has been reported in patients with CC RCC [2,6]. Due to the high proportion of patients in the International Metastatic RCC Database Consortium poor-risk group in Denmark, the response rates were expected to be closer to 10% [23].

The sample size calculation was based on the following assumptions: if the true ORR is 30%, then at least 30 patients are required to have an 80% probability of demonstrating that the ORR is greater than 10% at a 5% significance level.

The design of the study is not a randomized comparable study.

Ethics Approval

The INDIGO study has been approved by the National Committee on Health Research Ethics (approval number: H-19041833) and is being conducted in accordance with the Helsinki Declaration. Prior to study-related procedures, the patients must sign an informed consent from and must have received oral and written information about the study. The patients will be informed that they can withdraw their consent at any time without any consequences for their future treatment.

The study has been approved by the Danish Medicines Agency, follows the General Data Protection Regulation, and is registered at the Capital Region of Denmark (ID number: P-2019-232).

Results

The enrollment of patients started in March 2020, and until June 2022, a total of 9 patients have been included. The inclusion rate has been slower than first expected partly due to the COVID-19 pandemic and fewer patients being diagnosed with non-CC RCC than expected. When the study is completed, the results from the study will be published in international, peer-reviewed journals, and the Vancouver Declaration will be followed in all publications based on the study.

Discussion

Principal Findings

The INDIGO study will contribute knowledge about new treatments for a rare and heterogeneous group of patients with non-CC RCC and a poor prognosis. By using personalized medicine based on DNA mutations and gene profiles and by actively using ePROs, we hope to achieve an increase in the ORR. To our knowledge, there are no previous studies regarding treatments based on gene analyses and non-CC RCC or the combination of the active use of PROs and targeted therapy for patients with RCC. The interactive and real-time feedback with ePROs will benefit the patients, since the data will be used to improve the patients' trajectories. The use of ePROs gives clinicians better insight into patients' symptoms and side effects in the time between visits to the hospital.

As health care professionals, we should consider whether changing the limits between hospitals and homes (eg, with treatment-related apps on a patient's private phone) can reduce patients' quality of life. One can imagine that some patients will find it difficult to maintain their role as a patient when they are at home, while others will see the app, the questionnaires, and the active use of PROs as tools for gaining more influence on their supportive treatment and directing their conversations with health care professionals.

Comparison to Prior Work

In the INDIGO study, we will use ePROs both actively and passively. The active use of ePRO data can have a great impact on the course of treatment in terms of both the length of treatment and survival. By using ePROs, symptoms and side effects might be detected and treated at an earlier stage before they evolve to an extent that may necessitate a break in treatment or the discontinuation of medication. For some patients, longer treatment will result in longer overall survival. Basch et al [16,17] have shown significant benefits for survival and quality of life in a phase 3 study wherein patients undergoing treatment for metastatic cancer received weekly PRO monitoring. In Basch et al's [16,17] study, the median overall survival increased by 5.2 months in the PRO group when compared to that of the group receiving standard care, and 1-year survival increased by 6.5% in the PRO group.

Studies that achieve the successful use of ePROs are characterized by automated, severity-dependent patient advice, like those provided based on the alert algorithm in the INDIGO study. The patient advice will guide patients to either contact health care professionals or undergo self-management. Additionally, the health care professionals can access the patients' reports. In one study, depending on the severity reported, health care professionals had a predefined period in which to react [17,24-26].

Limitations

First, there are 14 different treatment options, including both immune-checkpoint inhibitors and tyrosine kinase inhibitors, among others, in the INDIGO study. Despite an overlap of side effects among the different treatments, a more specified questionnaire could have been developed for each treatment, which we expect could have been used to detect symptoms earlier. We chose the approach of providing an identical questionnaire to all patients with the expectation that the future will bring more individualized treatment strategies and a demand for a questionnaire that touches on many symptoms without being extensive.

Second, the selection of questions for the PRO questionnaire regarding symptoms and side effects in the INDIGO study is not based on a systematic methodology but is based on an expert group's assessment. A systematic methodology for the selection of PRO-related questions has previously been described in the literature [27].

Third, the small number of participants in the INDIGO study limits the power of the results regarding ePROs.

Conclusions

We believe that the addition of the active use of ePROs to the INDIGO study can improve the patients' trajectories. Our study will contribute further data on personalized medicine for rare types of RCC and provide new knowledge on symptoms reported directly by patients using eHealth tools.

Acknowledgments

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Data Availability

The study design and the small number of patients participating in the INDIGO study make it impossible to pseudonymize or anonymize data properly. This, in combination with the Danish interpretation of General Data Protection Regulation legislation, makes data sharing infeasible.

Conflicts of Interest

The INDIGO study is financially supported by Roche Pharmaceuticals and The Capital Region of Denmark. None of the authors are funded by Roche Pharmaceuticals.

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Abbreviations

CC: clear cell
CTCAE: Common Terminology Criteria for Adverse Events
EORTC: European Organization of Research in Treatment of Cancer
ePRO: electronic patient-reported outcome
HRQoL: health-related quality of life
ISO: International Organization for Standardization
ORR: overall response rate
PFS: progression-free survival
PRO: patient-reported outcome
PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
QLQ-C30: Quality of Life Questionnaire-C30
RCC: renal cell carcinoma
RECIST: Response Evaluation Criteria in Solid Tumors
TTF: time to treatment failure

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Protocol

Patient-Reported Outcome Dashboards Within the Electronic Health Record to Support Shared Decision-making: Protocol for Co-design and Clinical Evaluation With Patients With Advanced Cancer and Chronic Kidney Disease

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Abstract

Background: Patient-reported outcomes—symptoms, treatment side effects, and health-related quality of life—are important to consider in chronic illness care. The increasing availability of health IT to collect patient-reported outcomes and integrate results within the electronic health record provides an unprecedented opportunity to support patients' symptom monitoring, shared decision-making, and effective use of the health care system.

Objective: The objectives of this study are to co-design a dashboard that displays patient-reported outcomes along with other clinical data (eg, laboratory tests, medications, and appointments) within an electronic health record and conduct a longitudinal demonstration trial to evaluate whether the dashboard is associated with improved shared decision-making and disease management outcomes.

Methods: Co-design teams comprising study investigators, patients with advanced cancer or chronic kidney disease, their care partners, and their clinicians will collaborate to develop the dashboard. Investigators will work with clinic staff to implement the co-designed dashboard for clinical testing during a demonstration trial. The primary outcome of the demonstration trial is whether the quality of shared decision-making increases from baseline to the 3-month follow-up. Secondary outcomes include longitudinal changes in satisfaction with care, self-efficacy in managing treatments and symptoms, health-related quality of life, and use of

costly and potentially avoidable health care services. Implementation outcomes (ie, fidelity, appropriateness, acceptability, feasibility, reach, adoption, and sustainability) during the co-design process and demonstration trial will also be collected and summarized.

Results: The dashboard co-design process was completed in May 2020, and data collection for the demonstration trial is anticipated to be completed by the end of July 2022. The results will be disseminated in at least one manuscript per study objective.

Conclusions: This protocol combines stakeholder engagement, health care coproduction frameworks, and health IT to develop a clinically feasible model of person-centered care delivery. The results will inform our current understanding of how best to integrate patient-reported outcome measures into clinical workflows to improve outcomes and reduce the burden of chronic disease on patients and health care systems.

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KEYWORDS

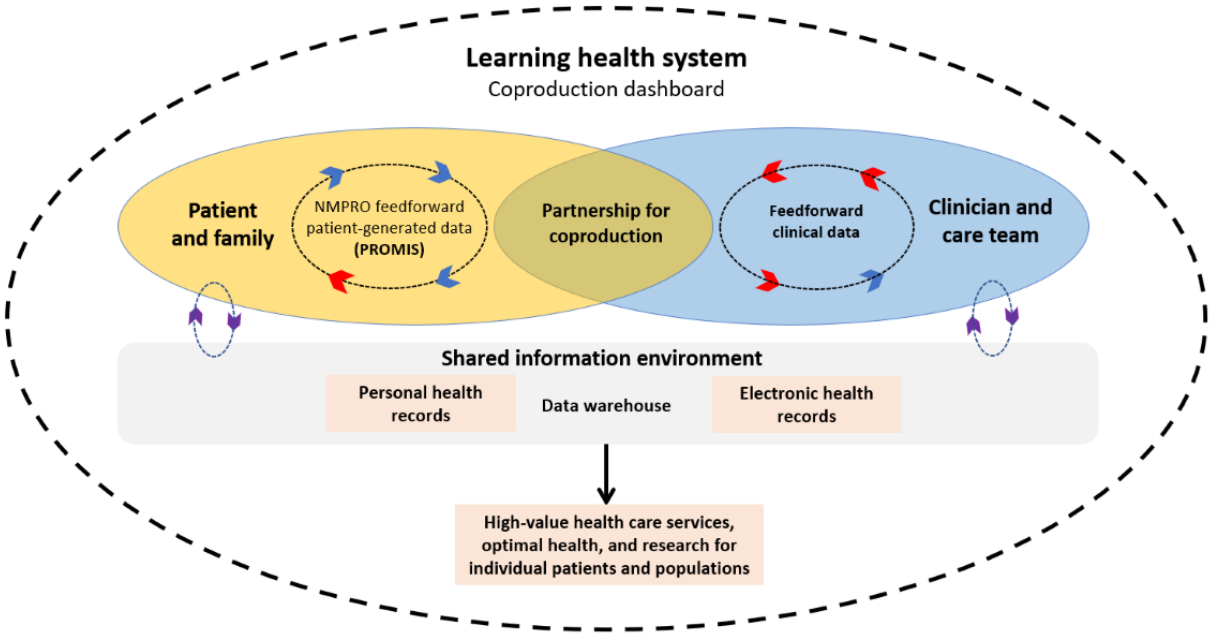
patient-reported outcome measures; shared decision-making; medical informatics; coproduction; learning health system; cancer; chronic kidney disease

Introduction

Background

Over half of Americans are currently living with a chronic illness such as cancer or chronic kidney disease [1,2], and supporting their symptom and care management needs is an urgent priority. Most patients living with a chronic illness experience distressing symptoms and side effects, most commonly fatigue, pain, and emotional distress such as fear or sadness [3-5]. Furthermore, these symptoms often go unrecognized by clinicians during regular visits [6,7], leading patients to experience chronically unmanaged symptoms that can escalate and increase the risk of potentially avoidable health care use [8,9]. Following distress screening guidelines from multiple organizations such as the Centers for Medicare and Medicaid Services [10,11], the National Comprehensive Cancer Network [12], and the Commission on Cancer [13], health care systems have begun to implement patient-reported outcome measures to facilitate more timely identification of symptom management needs. The most common strategies for implementing patient-reported outcome measures in clinical care involve feedback of results to clinicians to trigger clinical action such as referrals or feedback to patients to promote self-management of symptoms [14,15]. In this study, we will co-design and pilot-test an alternative system that will feed patient-reported outcome data back to patients *and* clinicians simultaneously through a shared interface to be used primarily during health care encounters (Figure 1). If implemented successfully, our approach has the potential to improve patient well-being and other clinical outcomes by supporting a collaborative health care communication and shared decision-making process [16-18].

Figure 1. Dartmouth coproduction model for clinical integration of patient-reported outcome measures (adapted from Nelson et al [17]). NMPRO: Northwestern Medicine Patient-Reported Outcomes; PROMIS: Patient-Reported Outcomes Measurement Information System.



Efforts to improve care delivery for advanced cancer and chronic kidney disease offer strong opportunities to develop and evaluate strategies for implementing patient-reported outcome measures. Medical advances in treatments have made it possible to live months or years with these diagnoses, meaning that patients need to manage their symptoms and treatments on a regular basis and across ongoing health care encounters [19,20]. Both diagnoses are accompanied by significant symptom burden [3], putting patients at risk of decreased health-related quality of life and increased health care expenditures. Currently, national costs associated with cancer and chronic kidney disease exceed US $100 billion per year, with most of those expenditures occurring during the advanced stages of both illnesses [21-23]. In addition, patients need to navigate complex and preference-sensitive decisions about their health care that involve considering their health-related quality of life priorities [24,25]. For instance, the decision to select treatments focused on extending life (eg, chemotherapy and dialysis) versus treatments focused on optimizing comfort (eg, best supportive care) requires thoughtful consideration of how one will feel in the future, both physically and emotionally, in response to treatment options [10,26]. Regularly monitoring patient-reported outcomes can also decrease the use of low-value health care services by creating opportunities for patients to discuss bothersome side effects with their clinicians and revisit alternative treatment options that might provide more value [10,27]. Therefore, incorporating patient-reported outcome measures into care for advanced cancer and chronic kidney disease can improve patients' health-related quality of life, align care provision with patient preferences and needs, and decrease the burden on the health care system by reducing unnecessary costly services.

Given these benefits, patient-reported outcome data can enhance the health care *coproduction* process [16]. Coproduction is an approach to health care delivery that posits that health care services and outcomes result from an interaction between clinician- and consumer-driven factors; thus, health care should be *coproduced* by patients, families, and health care professionals to achieve optimal health [16,28]. At the individual level, health care coproduction includes empowering patients and clinicians to *coassess* health status, *coplan* health care decisions, *co-design* acceptable and effective health services, and ultimately *co-deliver* those services [16,28]. As health IT has advanced, proponents have suggested that health care systems can encourage coproduction by implementing data visualization dashboards that are linked to the electronic health record and are accessible to both patients and clinicians [17,18,29,30]. These dashboards can display patient-generated data on symptoms, health-related quality of life, and goals of care along with key clinical data, allowing patients, care partners, and clinicians to view and discuss information together during and after scheduled visits (Figure 1). During in-clinic evaluations, patient-reported outcome clinical dashboards have demonstrated feasibility and acceptability, and preliminary evidence shows that dashboard users report higher-quality shared decision-making, a key process of coproduction, compared with nonusers [15,30-32]. However, no previous study has evaluated whether these dashboards are associated with changes from baseline to follow-up time points in shared decision-making and related disease management outcomes.

Objectives

This paper details the protocol for our study. We will design, implement, and longitudinally evaluate a clinician- and patient-facing dashboard for displaying patient-reported outcomes and other data from the electronic health record. The dashboard will be co-designed by patients and care partners, clinicians, and researchers to optimize the likelihood that it will be acceptable, feasible, and effective [33]. By fully integrating relevant information in a way that is easily viewed, discussed, and revisited by patients and clinicians, the dashboard may also promote other coproduction components such as symptom coassessment, coplanning through shared decision-making, and codelivery of health services by activating and empowering patients to self-manage their symptoms and care [16]. Although the study's primary focus is on enhancing the coproduction process for individual patients, the study falls within a quality improvement initiative that ultimately aims to achieve coproduction at the health care system level as well; situated within a learning health system, the dashboard implementation will continuously collect aggregated patient- and clinician-generated data to ensure that stakeholder perspectives are represented in system-wide policy decisions [17,29,34]. Therefore, the dashboard has the potential to improve health care system–level outcomes and care efficiency.

This study has two objectives: (1) to co-design a clinical dashboard that integrates patient-reported outcomes with other clinical data (eg, vital signs, laboratory tests, and medications) through the electronic health record and (2) to conduct a longitudinal demonstration trial evaluating whether the dashboard is associated with improved shared decision-making and disease management outcomes. Within objective 2, we hypothesize that patients who use the dashboard will experience increases from baseline to the 3- and 6-month follow-ups in perceived quality of shared decision-making, satisfaction with care, self-efficacy in managing treatments and symptoms, and health-related quality of life. We also hypothesize that, compared with historically and demographically matched controls, patients who use the dashboard will have a greater reduction in use of potentially avoidable, high-cost, and low-value health care services (see the Methods section for specific indicators that will be tested). By carefully delineating the dashboard design and evaluation process, this study will enable the dashboard's scalability and inform future investigations aiming to adapt the patient-reported outcome dashboard to other health care systems.

Methods

Ethics Approval

The Northwestern University Institutional Review Board approved all procedures described in this manuscript and a detailed data security plan (STU00210091, STU00211654, and STU00212634). Depending on the assessment point, survey data will be collected and stored securely through the health care system's electronic patient portal or through a REDCap (Research Electronic Data Capture; Vanderbilt University) [35]

server hosted at the Northwestern University Feinberg School of Medicine, both of which are protected by firewalls. Health service use data will be extracted from the Northwestern Medicine Enterprise Data Warehouse by trained Northwestern Medicine data analysts and entered into the study's REDCap database by the study coordinator (AC) approved by the ethics committee. Audio-recorded focus group data will be collected and stored in compliance with the Health Insurance Portability and Accountability Act. Audio files will be transcribed and deidentified, and transcriptions will be stored on a secure and password-protected Northwestern University Feinberg School of Medicine server accessible only to research staff listed on the study protocol approved by the ethics committee. After the transcription process is complete, all audio files will be deleted. All study procedures were considered low-risk by the Northwestern University Institutional Review Board, and the ethics review concluded that the benefits outweighed any minimal risks.

Objective 1: Dashboard Co-design Process

Clinical Setting

The dashboard will build on an existing infrastructure called the Northwestern Medicine Patient-Reported Outcomes system. This is the health care system's current technological framework for administering patient-reported outcome measures electronically and integrating data into the electronic health record to inform clinical care delivery [36]. Specifically, patients receive an email alert through their electronic patient portal 72 hours before an upcoming appointment, prompting a response to a patient-reported outcome questionnaire about symptoms and supportive care needs. To optimize measurement precision using as few items as possible, measures from the Patient-Reported Outcomes Measurement Information System (PROMIS) are used to assess anxiety, depression, pain, fatigue, and physical function. The electronic questionnaire automatically scores the patients' responses, stores them in the electronic health record, and generates alerts to their care team for any endorsed needs or clinically elevated symptoms.

In this study, this system will be adapted, with patient and other stakeholder input, into a clinical dashboard to facilitate symptom management and shared decision-making during scheduled health care visits for patients with advanced cancer and chronic kidney disease. Patient and care partner input will maximize the dashboard's patient-centeredness. By including clinicians in the design process, attention will be paid to the possible impact of dashboard participation on digital fatigue. To direct attention to and encourage discussion of the more potentially bothersome "hard-stop" alerts, alert thresholds on the patient-reported outcome measures will be set relatively high. The dashboard will be viewable by both patients (via the electronic patient portal) and physicians (via the health system's electronic health record software) and will automatically populate electronic health record–linked data, including patient-reported outcomes, laboratory test results, medications, and vital signs.

Participants and Eligibility Criteria

The first objective of the study is to collaborate with stakeholders who represent "end users" to co-design our clinical dashboard. End users include patients with advanced cancer or advanced chronic kidney disease, their care partners, and their clinicians. Clinician participants will include 2 oncologists (specializing in the treatment of gastrointestinal and lung cancer), a nephrologist, a nephrology physician assistant, and 2 primary care physicians. Patients will be eligible to participate if they have a history of receiving care from one or more of the participating clinicians at Northwestern Memorial Health Care. Patients with gastrointestinal cancer must have a confirmed diagnosis of stage 4 gastrointestinal cancer and have been receiving intravenous chemotherapy for at least three months. Patients with lung cancer must have a confirmed diagnosis of stage 3C or 4 lung cancer and have been receiving first- or second-line chemotherapy for at least 3 months. Patients with chronic kidney disease must have a confirmed diagnosis of at least stage 3 (defined as a clinical diagnosis or an estimated glomerular filtration rate of <60). Care partners will be eligible to participate if they assist in the care of a patient who would meet the inclusion criteria.

Procedures

For each of the two disease groups of interest (advanced cancer and chronic kidney disease), we will convene a co-design team comprising approximately 20 highly engaged stakeholders, including investigators, patients, care partners, clinicians, and health IT professionals. Co-design teams will iteratively develop the dashboard over the course of monthly meetings held during the first year of the study. Co-design meetings will involve team-based working sessions with predefined objectives and deliverables for each meeting (Table 1). The co-design process will occur in 4 broad phases informed by the Dartmouth Model for Co-design and Implementation (Figure 2 [37,38]), which has been successfully used to co-design and implement coproduction dashboards for people living with other chronic illnesses [31,32]. The 4 phases of co-design will include (1) defining the problem from the perspective of the end users, (2) understanding the context of use and lived experience, (3) building a design consensus, and (4) establishing and pilot-testing design specifications [37].

Table 1. Detailed outline of dashboard co-design session objectives.

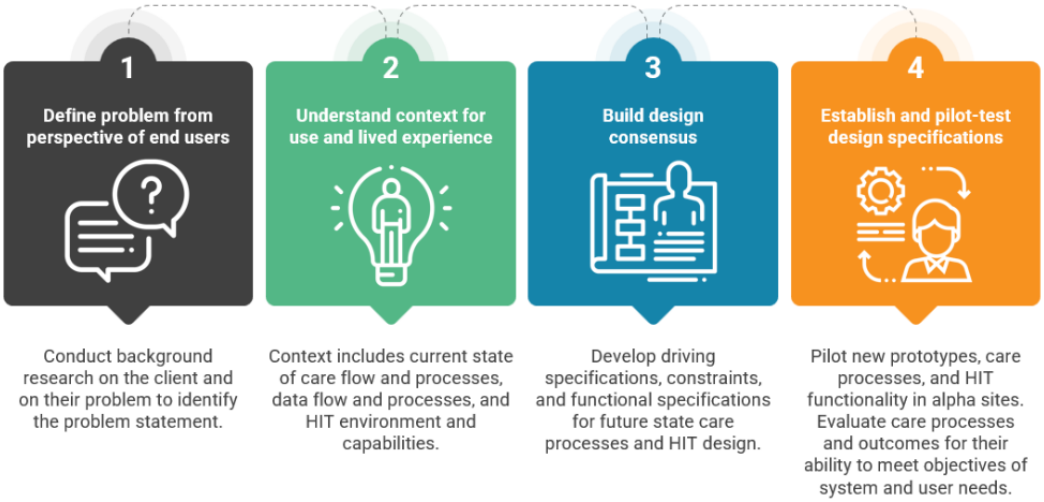
Activity	Co-design phase (Figure 2)	Objectives
Co-design launch meeting	1	• Introduction to the project and key concepts • Review of co-design working structure and scope of work
Working session 1	1 and 2	• Team building • Identifying facilitators of and barriers to shared decision-making and health coproduction • Exploring how better sharing of information can help
Working session 2	2	• Developing an understanding of how information can address facilitators of and barriers to improving care management
Working session 3	2 and 3	• Identifying common themes, priorities, and values regarding information and shared decision-making of dashboard end users • Developing team-specific co-design objectives
Working session 4	1, 2, and 3	• Refining team-specific objectives • Introducing options for data elements to populate dashboards • Envisioning dashboard
Working session 5	2, 3, and 4	• Exploring the use of a dashboard in a case example to advance emerging dashboard concepts
Working session 6	2, 3, and 4	• Exploring the use of a dashboard in a case example focused on a point of shared decision-making to advance emerging dashboard concepts
Working session 7	2 and 3	• Defining priority dashboard elements by dashboard user type • Proposing questions for external validation (focus groups) • Exchanging ideas and plans for dashboard concept between cancer and kidney disease teams
Working session 8	2 and 3	• Reviewing dashboard drafts and confirming alignment with co-design teams' visions • Reviewing data sources and measures to populate dashboards
Working session 9	2 and 3	• Reviewing feasible dashboard display options • Confirming completeness and appropriateness of planned data elements
Working session 10	2 and 3	• Demonstration of programmed dashboard display • Cancer and kidney disease co-design teams present respective dashboards and exchange ideas.
Working session 11	3 and 4	• Demonstration and critical review of fully programmed dashboards
Working session 12	2 and 3	• Interactive demonstration of fully programmed dashboards and questionnaires • Establishing specifications for alerts (symptom thresholds and routing) • Determining communication strategy and framing of patient-facing questionnaires
Working session 13 (physician champion working meeting)	2, 3, and 4	• Confirming final dashboard specifications • Demonstration and discussion of in-basket alerts • Confirming final patient dashboard user criteria • Confirming implementation workflows
Co-design wrap-up meeting	4	• Live demonstration of the prefinal dashboards and questionnaires • Conducting a reflection on the entire design process with respect to participation in co-design activities • Examining and discussing implications of COVID-19 and considerations for telehealth

Table 1 provides a detailed outline of the objectives of each co-design meeting. In phase 1 of the co-design process (defining the problem from the perspective of the end users), the investigators will introduce team members to the project and to the concepts of health care coproduction and shared decision-making. Team members will brainstorm facilitators of and barriers to shared decision-making and optimal care planning. In phase 2 (understanding the context of use and lived experience), co-design teams will discuss current clinical workflows for patient-reported outcome assessment and shared decision-making, brainstorm challenges and opportunities for solutions, and document end users' priorities for the dashboard's design and features. In phase 3 (building a design consensus), co-design meetings will focus on drafting, discussing, and

revising functional mock-ups of the dashboard, including design specifications and which clinical and patient-reported outcomes should be incorporated. Although patients will inform the specific symptoms and patient-reported outcomes that are important to assess, the investigators will select the appropriate measures for each outcome based on their measurement expertise. These will include measures from the Functional Assessment of Chronic Illness Therapy [39], PROMIS [40], and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [41]. In phase 4 (establishing and pilot-testing design specifications), co-design teams will provide iterative user experience feedback on the dashboard until its usability, feasibility, and compatibility with the electronic health record and clinical workflow systems are optimized. After each co-design meeting, the participants will be sent a brief survey via email to provide additional feedback.

In parallel to these intensive co-design team meetings, we will also hold supplemental focus groups. The primary purpose of these focus groups is to validate the evolving consensus and work product of the co-design teams with additional stakeholders. In tandem with phases 1 and 2 of co-design, we will conduct a focus group with 24 patients and care partners to gather an initial assessment of attitudes, beliefs, and perceptions to inform the dashboard's development. In tandem with phase 3 of co-design, we will conduct focus groups with a total of 72 stakeholders separated by disease group (cancer vs chronic kidney disease) and role (patients and care partners vs clinicians) to provide additional feedback on the appropriateness and desirability of the proposed dashboard design and content. In tandem with phase 4 of co-design, we will conduct focus groups to confirm the acceptability and usability of the dashboard (n=16-24 patients and care partners per disease group). Trained members of the research team will facilitate the discussions according to guides containing semistructured questions to follow in each session. Research staff will take notes during these sessions, which will also be audio recorded in case project staff are unable to manually document all responses.

Figure 2. Dartmouth model for dashboard co-design and implementation (reproduced from Coproduction Design and Implementation Flow by Van Citters [37], which is published under Creative Commons Attribution 4.0 International License [39]). HIT: health IT.



Outcomes

The primary outcome of the co-design process is to build a fully functional dashboard that can be implemented for clinical testing in objective 2 of this study. However, we also anticipate the development of a rich source of quantitative and qualitative data on the dynamics of development and implementation outcomes [42]. Data sources will include recordings and notes from the co-design meetings, focus groups, and postmeeting surveys. *Appropriateness* will capture stakeholders' perceptions of the compatibility between the proposed dashboard and the target clinical setting's goals and needs, whereas *feasibility* will assess perceptions of whether and how it can be successfully implemented into the clinical infrastructure. These 2 outcomes will be captured qualitatively through phase 1 and 2 co-design meetings and focus groups as well as through quantitative and qualitative responses provided by clinicians in a prelaunch survey conducted just before dashboard implementation. The *acceptability* of the near-final dashboard will reflect stakeholders' satisfaction with its design, content, and functionality. This outcome will be captured qualitatively through feedback provided during co-design meetings, co-design postmeeting surveys, and phase 4 focus groups' usability evaluations of the co-designed dashboard. The *fidelity* of the co-design process, or how well it was carried out as intended, will be assessed quantitatively through responses to postmeeting evaluations sent to each member of the co-design teams.

Analyses

Each of the outcomes will be summarized through qualitative analysis or descriptive statistics depending on the data type. For qualitative analyses, transcripts and notes from the sessions will be analyzed using a directed content analysis approach [43] guided by two established implementation science frameworks: the Consolidated Framework for Implementation Research [44] and the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework [45]. We will use a combination of traditional qualitative analysis and rapid qualitative analysis [46,47], which will allow investigators to provide rapid feedback to operational partners to inform the dashboard building and

implementation processes. Across the study phases, qualitative analyses will be conducted by approximately 5 to 7 coders trained in qualitative methods and relevant implementation frameworks. The team will establish coding frameworks or dictionaries (eg, by all coding an initial transcript, discussing and refining codes, and reaching a consensus about themes and categories). The remaining transcripts will then be double-coded and supervised by a lead team member. The full team will meet to discuss the final results to resolve any questions and elucidate the resultant themes. These strategies will be used to aggregate and summarize the main points and evaluate the relevant implementation outcomes (appropriateness, feasibility, and acceptability).

Objective 2: Demonstration Trial

Overview

The second objective of this study will include testing the co-designed dashboard in the flow of clinical care service delivery. First, as a quality improvement initiative, the dashboard will be implemented at the clinic level with all eligible patients who receive care from participating clinicians. This step will allow us to collect clinic-wide quality metrics associated with dashboard implementation. Second, the project will include a longitudinal follow-up study among a subset of patients to assess changes in patient outcomes associated with using the dashboard. Figure 3 shows the flow diagram of the dashboard's clinical implementation and evaluation. Table 2 provides a schedule of the survey measures completed by the patients at each assessment point of the demonstration trial. These procedures and measures are described in more detail in the following sections.

Figure 3. Demonstration trial flow diagram.

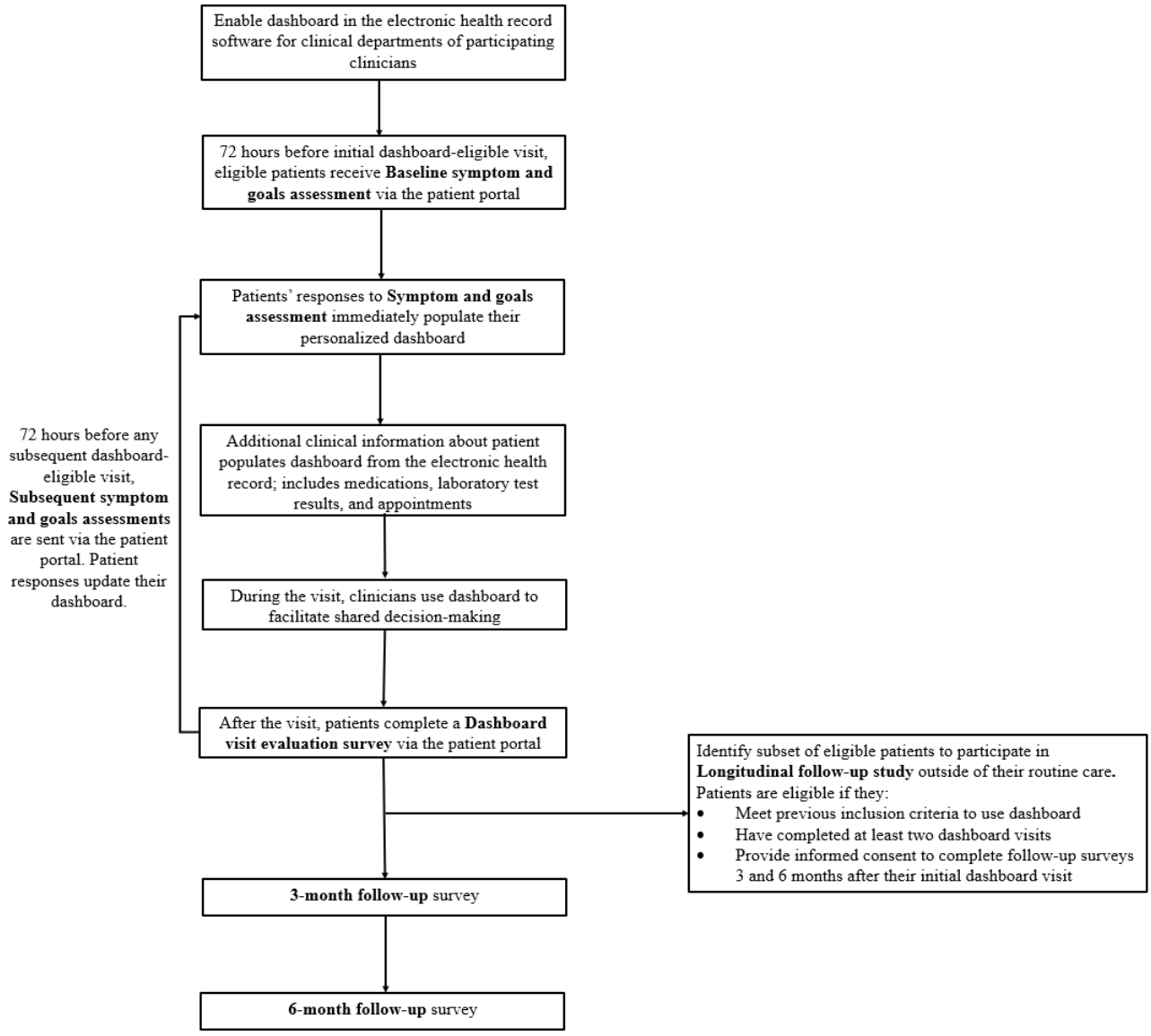


Table 2. Schedule of survey measures in demonstration trial[a].

Domain and subdomains	Baseline symptom and goals assessment	Subsequent symptom and goals assessments	Dashboard visit evaluation	3-month follow-up	6-month follow-up
Patient measures					
Sociodemographic data	Age, gender, race, ethnicity, marital status, employment, and education	—[b]	—	—	—
Goals of care	De novo measure	De novo measure	—	—	—
Health-related quality of life					
Health perception	PROMIS[c] Global01 [40]	PROMIS Global01	—	—	—
Global	FACT-G7[d] [48]	FACT-G[e] GF7[f] item [48]	—	FACT-G7	FACT-G7
Fatigue	PROMIS 2-item custom SF[g] [49]	PROMIS 2-item custom SF	—	PROMIS CAT[h] [49]	PROMIS CAT
Anxiety	PROMIS 2-item custom SF [50]	PROMIS 2-item custom SF	—	PROMIS CAT [50]	PROMIS CAT
Pain	PROMIS 2-item custom SF [51]	PROMIS 2-item custom SF	—	PROMIS CAT [51]	PROMIS CAT
Depression	PROMIS 2-item custom SF [50]	PROMIS 2-item custom SF	—	PROMIS CAT [50]	PROMIS CAT
Physical function	PROMIS 2-item custom SF [52]	PROMIS 2-item custom SF	—	PROMIS CAT [52]	PROMIS CAT
Shortness of breath	PROMIS DYSSV014 item [53]	PROMIS DYSSV014 item	—	—	—
Urinary frequency (chronic kidney disease only)	PRO-CTCAE[i] 63[a] item [41]	PRO-CTCAE 63[a] item	—	—	—
Edema	PRO-CTCAE 22[b] item [41]	PRO-CTCAE 22[b] item	—	—	—
Nausea	PROMIS GISX49 item [54]	PROMIS GISX49 item	—	—	—
Appetite	PROMIS GISX55 item [54]	PROMIS GISX55 item	—	—	—
Itching (chronic kidney disease only)	PROMIS PIQSeverity04 item [55]	PROMIS PIQSeverity04 item	—	—	—
Neuropathy (cancer only)	FACT[j] and GOG-NTX-4[k] (version 4) [56]	FACT and GOG-NTX-4 (version 4)	—	—	—
Constipation (cancer only)	PRO-CTCAE 15[a] item [41]	PRO-CTCAE 15[a] item	—	—	—
Diarrhea (cancer only)	PROMIS GISX38 item [54]	PROMIS GISX38 item	—	—	—
Side effect bother	FACT-G GP5[l] item [39]	FACT-G GP5 item	—	—	—
Shared decision-making	CollaboRATE [57]	—	CollaboRATE	CollaboRATE	CollaboRATE
Self-efficacy-managing treatments	PROMIS 4-item custom SF [58]	—	—	PROMIS 4-item custom SF	PROMIS 4-item custom SF
Self-efficacy-managing symptoms	PROMIS 3-item custom SF [58]	—	—	PROMIS 3-item custom SF	PROMIS 3-item custom SF
Treatment satisfaction	FACIT-TS[m] TS40 item [59]	—	FACIT-TS TS40 item	FACIT-TS TS40 item	FACIT-TS TS40 item
Treatment satisfaction (cancer only)	CAHPS[n] Cancer Care Survey [60]	—	—	CAHPS Cancer Care Survey	CAHPS Cancer Care Survey

Domain and subdomains	Baseline symptom and goals assessment	Subsequent symptom and goals assessments	Dashboard visit evaluation	3-month follow-up	6-month follow-up
Health care communication	CASE[o] (information factor) [61]	—	—	CASE (information factor)	CASE (information factor)
Medication adherence	PMAS[p] [62]	—	—	PMAS	PMAS
Social isolation	PROMIS UCLA[q] 14x2 item [63]	—	—	PROMIS UCLA 14x2 item	PROMIS UCLA 14x2 item
Health literacy	SILS[r] [64]	—	—	SILS	SILS
Financial toxicity	COST[s]-FACIT[t] FT12 item [65]	—	—	COST-FACIT FT12 item	COST-FACIT FT12 item
Usability, acceptability, and adoption	—	—	—	SUS[u] [66], SPHERE[v] [67], and NoMAD[w] [68]	SUS, SPHERE, and NoMAD
Fidelity of dashboard use	—	—	De novo item	—	—
Clinician measures					
Usability, acceptability, and adoption	—	—	—	SUS, SPHERE, and NoMAD	SUS, SPHERE, and NoMAD
Fidelity of dashboard use	—	—	—	De novo item	De novo item
Dashboard sustainability	—	—	—	—	CSAT[x] [69]

[a]Single-item names were obtained from the referenced parent measures or item banks.

[b]Empty cells indicate that a given domain was not included at that particular assessment point.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

[d]FACT-G7: Functional Assessment of Cancer Therapy-General, 7-item version.

[e]FACT-G: Functional Assessment of Cancer Therapy-General.

[f]GF7: FACT-G global quality of life item.

[g]SF: short form.

[h]CAT: computerized adaptive test.

[i]PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

[j]FACT: Functional Assessment of Cancer Therapy.

[k]GOG-NTX-4: Gynecologic Oncology Group-Neurotoxicity.

[l]FACT-G GP5: FACT-G side effect bother item.

[m]FACIT-TS: Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction.

[n]CAHPS: Consumer Assessment of Health Plans Study.

[o]CASE: Communication and Attitudinal Self-Efficacy scale.

[p]PMAS: PROMIS Medication Adherence Scale.

[q]UCLA: University of California, Los Angeles.

[r]SILS: Single Item Literacy Screener.

[s]COST: Comprehensive Score for Financial Toxicity.

[t]FACIT: Functional Assessment of Chronic Illness Therapy.

[u]SUS: System Usability Scale.

[v]SPHERE: Stroke Prevention in Healthcare Delivery Environments study.

[w]NoMAD: Normalization Measure Development.

[x]CSAT: Clinical Sustainability Assessment Tool.

Procedures

Clinic-Wide Dashboard Implementation

The co-designed dashboard will be enabled in the health system's electronic health record software within the clinical departments of all participating clinicians. The first month of dashboard implementation will constitute a "soft launch" period where participating clinicians and their eligible patients will be trained on using the dashboard and will work with the project team to troubleshoot and resolve any technical and practical issues. After the soft launch period, clinicians will be encouraged to use the dashboard during clinical encounters with all their patients who meet the inclusion criteria (as described previously in objective 1). As outlined in Figure 3, eligible patients will receive a baseline symptom and goals assessment (see Table 2

for specific measures) through the electronic patient portal approximately 72 hours before their initial dashboard-eligible visit. If a patient does not respond to the symptom and goals assessment at home, the study staff will assist patients to complete it over the telephone or in-clinic before the appointment. Responses to the symptom and goals assessment, in addition to their most recent results on other clinical data, will populate the dashboard in real time. Clinicians will use the dashboard during the upcoming visit to improve communication and shared decision-making with patients. Following the visit, patients will receive a dashboard visit evaluation survey through the electronic patient portal to provide feedback on their care experience and the shared decision-making process that occurred during their visit. This process will be repeated for any subsequent visit that a patient has with their participating clinician during the study period.

Dashboard Content

The dashboard will display results from the patient's most recent symptom and goals assessment and other clinical measures stored in the electronic health record. The included assessments will be determined through extensive stakeholder input during the dashboard co-design process described in objective 1. The symptom and goals assessment will include a mix of items and scales selected to optimize clinical relevance and feasibility. For instance, each assessment will include the PROMIS Global01 health perception item [40], the Functional Assessment of Cancer Therapy-General (FACT-G) GF7 global quality of life item [39], and the FACT-G GP5 side effect bother item [39]. Two-item PROMIS custom short forms will assess anxiety [50], depression [50], fatigue [49], pain [51], and physical function [52]. Additional symptoms will mostly be assessed with single items, for example, the PROMIS DYSSV014 dyspnea item [53], the PRO-CTCAE 63a urinary frequency item (chronic kidney disease only) [41], or the PRO-CTCAE 15a constipation item (cancer only) [41]. Table 2 provides a complete list of health-related quality of life measures to be included in each symptom and goals assessment, and the results will be displayed within the dashboard in a user-friendly format.

In addition to rating health-related quality of life domains, patients will respond to 5 open-response questions in the symptom and goals assessment regarding their goals of care that will populate the dashboard. These questions will prompt patients to specify (1) the top 1 or 2 concerns they would like to discuss during the visit, (2) their most concerning side effects, (3) overall goals regarding their cancer or kidney disease treatment, (4) personal goals and values, and (5) how they can work together with their care team to achieve their goals. Finally, the dashboard will display the most recent results on other clinical measures typically collected during the care process and stored within the electronic health record. For patients with cancer, the additional clinical data will include medications, weight, white blood cell count, absolute neutrophils, hemoglobin, albumin, and an appointment schedule. For patients with chronic kidney disease, the additional clinical data will include weight, blood pressure, glomerular filtration rate, hemoglobin A1c, microalbuminuria, urine protein, and an appointment schedule. Patients and clinicians will view the patient's individualized dashboard on a computer screen during the visits. Patients will also be able to view their dashboard in between visits using their own devices (eg, computer, tablet, and mobile phone) that can access their electronic patient portal.

Longitudinal Follow-up Study

To assess the longitudinal changes in our primary and secondary study outcomes, a subset of approximately 200 patients will participate in a longitudinal follow-up study. Patients will be eligible to participate if they meet all other study inclusion criteria, have completed at least two dashboard-eligible visits, and provide informed consent to complete a follow-up survey at 3 and 6 months. In parallel to collecting these follow-up patient outcomes, all participating clinicians will also complete surveys at 3 and 6 months to report on their experience with the dashboard's implementation (Table 2). All survey data collected during the longitudinal follow-up study will be collected outside the electronic patient portal using a web-based survey platform (REDCap) [35].

Dashboard-Naïve Comparison Group

For analyses focusing on health service use (see outcome description in the Health Service Use section), we will identify two cohorts of patients who were not exposed to the dashboard: (1) a cohort of eligible patients with cancer and chronic kidney disease who received care concurrently from participating Northwestern Medicine clinicians but who did not enroll in the dashboard study and (2) a matched cohort of patients with cancer and chronic kidney disease treated contemporaneously by nonparticipating Northwestern Medicine clinicians. Health service use variables will be the only study outcome data available for these 2 comparison groups.

Primary Study Outcome

The central outcome of the study is shared decision-making in the treatment of patients with advanced cancer or chronic kidney disease. We will use the CollaboRATE measure [57] to assess patients' perceptions of the quality of shared decision-making occurring in patient-clinician interactions. Patients will complete the measure at baseline, 3-month follow-up, and 6-month follow-up. In addition, they will respond to the CollaboRATE measure in each dashboard visit evaluation survey to assess the perceived quality of shared decision-making that occurred during each dashboard visit. CollaboRATE is a validated 3-item measure that was developed with significant patient input and asks patients to rate the extent to which their clinicians helped them understand health issues, how much effort was made to listen to their priorities, and how much effort was made to include their priorities in treatment selection. We will use the 5-category response scale version (0="No effort was made," 1="A little effort was made," 2="Some effort was made," 3="A lot of effort was made," and 4="Every effort was made"). Scores will be generated by summing responses to the 3 items and generating a score ranging from 0 to 12, with higher scores indicating greater shared decision-making. The CollaboRATE measure is generic and, therefore, it is appropriate for use with patients with various chronic conditions.

Secondary Study Outcomes

Satisfaction With Health Care Quality

Satisfaction with health care will be assessed at baseline, 3 months, and 6 months with a single item from the Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction measure [59]. Patients will also respond to the item in each dashboard visit evaluation survey to assess their satisfaction with the dashboard visit. Patients will complete item TS40—"How do you rate the care you received?"—on a scale of 0 (poor) to 4 (excellent). The scale has met psychometric standards for a variety of chronic health conditions [59]. In addition, 5 items from the Consumer Assessment of Health Plans Study Cancer Care Survey, Drug Therapy Version [60], will be assessed at baseline, 3 months, and 6 months among patients with cancer only. These items measure patients' experiences with cancer care. For example, the item "In the last 6 months, did your drug therapy team advise you about or help you deal with these changes in your energy levels?" is rated as 1 (Yes, definitely), 2 (Yes, somewhat), or 3 (No).

Self-efficacy for Managing Chronic Conditions

A total of 2 subdomains of the PROMIS Self-Efficacy for Managing Chronic Conditions domain will be assessed at baseline and at the 3- and 6-month follow-ups. A 4-item custom short form created from the PROMIS Self-Efficacy for Managing Medications and Treatment Item Bank version 1.0 [58] will assess patients' confidence in their ability to follow treatment and medication plans. A 3-item custom short form created from the PROMIS Self-Efficacy for Managing Chronic Conditions-Managing Symptoms Item Bank version 1.0 [58] will assess confidence in their ability to manage their symptoms outside of their health care encounters. Sample items include "I can fit my medication schedule into my daily routine" (self-efficacy for managing treatment and medication) and "I can manage symptoms when I am at home" (self-efficacy for managing symptoms). Similar to all PROMIS measures, these measures are scored on a T-score metric with a mean of 50 and SD of 10. Higher scores indicate more of the construct being measured. These PROMIS measures have all demonstrated reliability, precision, and construct validity based on their correlation with legacy instruments [58].

Health-Related Quality of Life

To evaluate changes in health-related quality of life as an outcome associated with using the dashboard, a subset of health-related quality of life domains included in the symptom and goals assessment will be assessed again at the 3- and 6-month follow-ups (see Table 2 for a schedule of assessments). To assess changes in global health-related quality of life, patients will respond to the 7-item version of the FACT-G [48] in the baseline symptom assessment and in the 3- and 6-month follow-up surveys. The 7-item version of the FACT-G was derived from the 28-item version of the FACT-G [39] to offer a brief yet comprehensive assessment of multiple health-related quality of life domains relevant to patients with cancer. It has demonstrated adequate to good reliability, evidence of construct validity (convergent and known groups), and responsiveness to changes in health associated with an intervention [48,70]. To evaluate changes from baseline in core symptoms, the 3- and 6-month follow-up surveys will also contain computerized adaptive tests of the PROMIS anxiety [50], depression [50], fatigue [49], pain [51], and physical function [52] item banks.

Health Service Use

After study completion, we will retrospectively extract data on the use of potentially avoidable, high-cost, or low-value health care services from the periods 6 months before and 6 months after the first dashboard use. Specific indicators will include (1) unplanned all-cause hospital admissions, (2) potentially avoidable all-cause emergency department use, (3) excess (all-cause) days in acute care within 30 days of hospital discharge, and (4) 7-day readmissions. In addition, among patients with cancer, we will assess the following disease-specific indicators: (5) admissions and emergency department visits for patients receiving outpatient chemotherapy, (6) chemotherapy within the last 14 days of life, (7) use of a triage clinic, (8) completion of an advance directive, and (9) hospice use of >3 days. Among patients with chronic kidney disease, the following additional indicators will be collected: (10) use of emergency start dialysis; (11) chronic kidney disease–related emergency department or inpatient use; and (12) progression from chronic kidney disease stage 3 to stage 4, stage 4 to stage 5, or stage 3 to stage 5.

Implementation Outcomes

Patient- and clinician-reported survey measures will capture relevant implementation outcomes [42] of the demonstration trial supplemented by data from the electronic health record and qualitative data gathered by the study staff throughout the project. To assess the project's *reach*, we will extract data from the electronic health record on patient enrollment rates in the demonstration trial and response rates to the symptom and goals assessments. To assess the *fidelity* of the dashboard's use during the study period, patients will report whether the dashboard was discussed during their eligible clinical encounter in each dashboard visit evaluation survey, which is completed immediately after the appointment. Moreover, the study staff will conduct regular clinician observations to assess whether the dashboard is being used consistently and as intended. To assess *adoption*, clinicians will self-report in their 3- and 6-month surveys the frequency with which they use the dashboard with eligible patients. To assess *usability*, *acceptability*, and *adoption*, both patients and clinicians will rate the dashboard at the 3- and 6-month follow-ups on the System Usability Scale [66], the Stroke Prevention in Healthcare Delivery Environments study acceptability measure [67], and the Normalization Measure Development measure of adoption of new health care elements [68]. Finally, clinicians will rate the perceived *sustainability* of the clinical dashboard at the 6-month follow-up using the Clinical Sustainability Assessment Tool [69]. In addition to these implementation outcomes, we will closely document the implementation process, including strategies that were used to successfully carry out the project and implement the dashboard. These may include, but are not limited to, strategies for stakeholder engagement and co-design, patient recruitment and outreach, and training resources for using the dashboard to facilitate shared decision-making. Quantitative data will be analyzed using descriptive statistics,

and qualitative data will be analyzed using the approaches described in objective 1.

Statistical Analyses

For all statistical tests, a nominal 2-sided *P* value of <.05 will be considered statistically significant. Unless otherwise noted, analyses will be conducted on the full analysis set and stratified by populations with chronic kidney disease versus cancer.

The primary analyses for objective 2 are within-group mean changes in shared decision-making (CollaboRATE), self-efficacy for managing chronic conditions (PROMIS), satisfaction with care (Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction and Consumer Assessment of Health Plans Study Cancer Care Survey), and health-related quality of life and symptoms (PROMIS, Functional Assessment of Chronic Illness Therapy, and PRO-CTCAE). First, we will test whether within-group means have changed significantly from the baseline and symptom assessments (as appropriate) to the 3-month follow-up (primary) and 6-month follow-up (secondary) using paired samples *t* tests. We will supplement the paired *t* tests with multivariable regression models to adjust for key covariates (eg, demographic and clinical characteristics). Regarding health service use, we will first use paired-sample *t* tests to compare rates in the occurrence of each indicator described in the Health Service Use outcome section between the 6 months before and after the date of first dashboard exposure. On a secondary basis, we will model these outcomes as count variables using zero-inflated Poisson regression to adjust for covariates [71,72]. Finally, we will compare rates of health service use before and after the first dashboard exposure between patients exposed to the dashboard and the naïve comparison cohorts using 2-sample *t* tests and zero-inflated Poisson regression. To do so, we will use propensity score matching to create comparable cohorts of patients with and without exposure to the dashboard. We will match on age, sex, cancer type (where applicable), and disease severity or staging [73].

Power and Sample Size Calculations

Sample size considerations for objective 2 were informed by statistical power analyses for differences in within-group changes in mean responses to the CollaboRATE shared decision-making measure and PROMIS measures from baseline to the 3-month follow-up. Within-group mean changes in the CollaboRATE 5-point response scale version ranged from approximately 2.0 to 4.5, with SDs of approximately 3.5 [74]. For the CollaboRATE measure, we conducted a statistical power analysis making the following conservative assumptions: (1) a correlation between baseline and 3-month follow-up scores of r=0.30; (2) a common SD of 3.5 points; (3) a 2-sided *P* value of .05; and (4) mean changes of 1.0, 1.5, and 2.0 points. These analyses suggested that sample sizes of 137, 62, and 36 patients would be needed to detect mean changes of 1.0, 1.5, and 2.0 points, respectively, using a paired *t* test.

As noted in the Methods section, all PROMIS measures are scored as a T-score metric with a mean of 50 and SD of 10. Changes as low as 3 points can be clinically meaningful [75]. For power analysis regarding PROMIS measures, we made the following conservative assumptions: (1) a correlation between baseline and 3-month follow-up scores of r=0.50; (2) a common SD of 10.0 points; (3) a 2-sided *P* value of .05; and (4) mean changes of 3.0, 4.0, and 5.0 points. These analyses suggested that sample sizes of 90, 52, and 34 patients would be needed to detect mean changes of 3.0, 4.0, and 5.0 points, respectively, using a paired *t* test.

Results

The co-design sessions (objective 1), which focused on collaboratively designing the dashboard's content and format for initial clinical testing, concluded in May 2020. Focus groups supplementing the co-design sessions were completed in October 2019, February 2020, and October 2021. Data collection for the demonstration trial is anticipated to be completed by the end of July 2022. Study investigators currently meet monthly as an entire team to discuss progress on manuscript development for results dissemination. Each study objective will have at least one resulting publication: (1) co-design process and outcomes and (2) demonstration trial process and outcomes.

Discussion

Overview

In this study, we hypothesize that co-designing and implementing a patient-reported outcome clinical dashboard will be associated with improved processes underlying health care coproduction among adults with advanced cancer or chronic kidney disease, including shared decision-making, satisfaction with care, engagement in health care, self-efficacy in managing symptoms and treatments, health-related quality of life, and use of health services. Collaborating with patients, care partners, and clinicians to create scalable clinical dashboards can help improve coproduction outcomes [31,33]. Thus, this study draws upon a co-design framework to actively engage patients and care partners in the iterative design and evaluation of a patient-reported outcome dashboard to be used during clinical encounters with patients with advanced cancer and chronic kidney disease. However, few previous studies have attempted to improve the coproduction process by integrating patient-reported outcomes with other electronic health record–linked clinical results in a data visualization platform to facilitate shared decision-making [15,31,32]. In particular, our dashboard aims to improve recognition and shared decision-making for the management of patients' symptoms and treatment needs, which can promote more effective use of the health care system and translate into improved patient outcomes [17,18,29,76].

Strengths

The dashboard's design and evaluation processes have several strengths worth noting. First, the dashboard will be co-designed by investigators and key stakeholders (patients, care partners, and clinic staff). Collaborating with stakeholders promotes person-centered care delivery and increases the likelihood that a new health care element can be successfully implemented and optimally impactful [33]. Unfortunately, stakeholder engagement is often skipped when developing interventions owing to time

and money constraints [77]. Second, we will carefully document each step of the dashboard design and implementation process, including any unanticipated modifications needed for improving its acceptability, feasibility, and adoption. This will ensure that the dashboard can be easily disseminated to other investigators and adopted by other health care systems and that the study can be replicated. Third, the dashboard is designed to be dynamic and individualized. It will be fully integrated within the electronic health record, providing a more complete picture of a patient's health status and facilitating informed decision-making and treatment planning by displaying patient-reported outcomes along with other clinical data. New data populate the dashboard in real time so that health care can efficiently adapt to patients' changing symptom and care needs. Fourth, patients can view the dashboard at any time through their electronic patient portal, which will display symptom scores over time in user-friendly graphs. This will allow patients who do not complete regular health care visits to still experience benefits through enhanced self-reflection and self-monitoring of personalized symptom feedback even if explicit health care decision-making does not occur. In summary, our patient-centered dashboard and design process provide an efficient, feasible, and scalable model for integrating patient-reported outcome data collection into person-centered, value-based care delivery.

Limitations

Despite these strengths, this project has limitations that warrant discussion. First, the study will focus only on patients in the advanced stages of 2 chronic conditions and on those who regularly access their electronic patient portals. Although advanced cancer and chronic kidney disease are two of the most common and burdensome illnesses to individuals and the health care system [3,21,23], we are actively expanding the dashboard into other areas of medicine such as rheumatology. Second, the electronic health record software in which the dashboard will be developed has limitations in how data are visualized, which limits the opportunities for user-centered design. Nonetheless, integration into the electronic health record will allow us to improve other aspects of the user experience, including reducing the clinical burden that might be associated with using an external system, providing a shared dashboard environment that is accessible to both patients and clinicians, and allowing patient-reported outcome results to be integrated with other routinely collected health information. Third, the dashboard will be evaluated using a single-arm design, precluding the ability to draw causal conclusions about any observed changes in patient outcomes during the demonstration project. Fourth, the dashboard and study process will only be available in English and may underrepresent people with low health literacy and less digital acumen or computer access. Future efforts will need to adapt the dashboard to other languages, chronic illness groups, and health ITs represented in the local health care system. There may also be an opportunity in the future to conduct a formal randomized controlled trial of the dashboard's efficacy.

This study demonstrates how to combine stakeholder engagement, a health care coproduction framework, and health IT to develop a clinically feasible, acceptable, and scalable model of patient-centered care delivery. This study's premise integrates emerging research indicating that better patient outcomes and appropriate health care use can be enhanced through patient-clinician collaboration in the context of well-designed workflows and systems. Thus, this study focuses on dealing with the manifold challenges of implementing significant changes in workflow and clinical approach in the real world of ambulatory care of patients with a serious chronic illness. We aim to build on implementation research to understand the needed adoption, acceptability, and feasibility of new tools to optimize a successful and sustainable transformation of the clinical encounter over time. Our work serves as an example for transforming care delivery in a way that embraces value-based care and has the potential to improve the lives of patients with chronic conditions.

Acknowledgments

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Data Availability

Although we have collected data for this study, this manuscript does not report any results. Our intention is to share data associated with the published results as they emerge.

Conflicts of Interest

AH is a health care consultant for the Yale New Haven Health System Center for Outcomes Research and Evaluation, where she is involved in re-evaluation activities for the Centers for Medicare and Medicaid value-based payment programs. Neither the Yale New Haven Health System Center for Outcomes Research and Evaluation nor the Centers for Medicare and Medicaid provided support or funding for this work.

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Abbreviations

FACT-G: Functional Assessment of Cancer Therapy-General
PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture

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Protocol

Acceptability and Feasibility of the Telehealth Bariatric Behavioral Intervention to Increase Physical Activity: Protocol for a Single-Case Experimental Study

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Abstract

Background: Regular physical activity (PA) is recommended to optimize weight and health outcomes in patients who have undergone metabolic and bariatric surgery (MBS). However, >70% of patients have low PA levels before MBS that persist after MBS. Although behavioral interventions delivered face-to-face have shown promise for increasing PA among patients who have undergone MBS, many may experience barriers, preventing enrollment into and adherence to such interventions. Delivering PA behavior change interventions via telehealth to patients who have undergone MBS may be an effective strategy to increase accessibility and reach, as well as adherence.

Objective: This paper reports the protocol for a study that aims to assess the feasibility and acceptability of the protocol or methods and the Telehealth Bariatric Behavioral Intervention (TELE-BariACTIV). The intervention is designed to increase moderate-to-vigorous intensity PA (MVPA) in patients awaiting bariatric surgery and is guided by a multitheory approach and a patient perspective. Another objective is to estimate the effect of the TELE-BariACTIV intervention on presurgical MVPA to determine the appropriate sample size for a multicenter trial.

Methods: This study is a multicenter trial using a repeated (ABAB'A) single-case experimental design. The A phases are observational phases without intervention (A1=pre-MBS phase; A2=length personalized according to the MBS date; A3=7 months post-MBS phase). The B phases are interventional phases with PA counseling (B1=6 weekly pre-MBS sessions; B2=3 monthly

sessions starting 3 months after MBS). The target sample size is set to 12. Participants are inactive adults awaiting sleeve gastrectomy who have access to a computer with internet and an interface with a camera. The participants are randomly allocated to a 1- or 2-week baseline period (A1). Protocol and intervention feasibility and acceptability (primary outcomes) will be assessed by recording missing data, refusal, recruitment, retention, attendance, and attrition rates, as well as via web-based acceptability questionnaires and semistructured interviews. Data collected via accelerometry (7-14 days) on 8 occasions and via questionnaires on 10 occasions will be analyzed to estimate the effect of the intervention on MVPA. Generalization measures assessing the quality of life, anxiety and depressive symptoms, and theory-based constructs (ie, motivational regulations for PA, self-efficacy to overcome barriers to PA, basic psychological needs satisfaction and frustration, PA enjoyment, and social support for PA; secondary outcomes for a future large-scale trial) will be completed via web-based questionnaires on 6-10 occasions. The institutional review board provided ethics approval for the study in June 2021.

Results: Recruitment began in September 2021, and all the participants were enrolled (n=12). Data collection is expected to end in fall 2023, depending on the MBS date of the recruited participants.

Conclusions: The TELE-BariACTIV intervention has the potential for implementation across multiple settings owing to its collaborative construction that can be offered remotely.

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KEYWORDS

behavior change intervention; bariatric surgery; physical activity; telehealth; single-case experimental design; self-determination; self-efficacy; behavior change techniques; mobile phone

Introduction

Background

Severe obesity (class II and III; BMI ≥35 kg/m^2) affects approximately 9.5% of Canadians [1]. Metabolic and bariatric surgery (MBS) is generally effective in inducing significant and lasting weight loss [2] while reducing the costs related to severe obesity and associated complications [3,4]. MBS offers significant health benefits and improves the quality of life [4,5]. The number of procedures performed worldwide has increased during the last decade in particular, reaching almost 700,000 surgeries performed in 2018 [6]. However, approximately half of the patients who have undergone MBS regain at least 10% and 20% of their maximum weight loss 1 year and 5 years after reaching their nadir weight, respectively [7].

In the context of MBS, physical activity (PA) is recommended given its multiple benefits [8,9]. Studies have shown that pre- and post-MBS PA can improve physical fitness, cardiometabolic health, quality of life, and depressive symptoms [10-17]. However, 70% to 95% of adults are inactive before MBS and remain so after MBS [18,19]. Thus, there is a need to develop interventions with the aim of increasing pre- and post-MBS PA. Introducing PA behavior change interventions before MBS with additional support offered after MBS seems to be an ideal approach to optimize MBS benefits and provide transitional support toward post-MBS lifestyle [20]. The most compelling evidence to support this assertion comes from studies that have shown that PA interventions delivered before MBS can increase PA until 1 year after MBS [21,22]. Furthermore, pre-MBS PA can improve physical fitness, which may help reduce perioperative complications and length of hospital stay [23]. Finally, participants' motivation and readiness for PA increased close to their surgical date [24].

Supervised exercise within the context of clinical- and research-based interventions, although effective in conferring health benefits, does not increase long-term PA in adults undergoing MBS [17,25,26], likely because this type of intervention almost never includes behavioral change methods (ie, no target of PA determinants such as self-determination and self-efficacy that may help with maintenance of PA behavior). Interventions that apply methods specifically targeting PA determinants are needed to equip adults with the knowledge, skills, and confidence to engage in regular PA on their own, as resources are not infinite. Therefore, PA behavior change interventions should be considered, which can be effective in increasing PA in adults with obesity [27]. In adults undergoing MBS, Bond et al [22,28,29] have shown that BariActiv, a 6-week intervention delivered before MBS, which included weekly one-on-one meetings and focused on behavior change techniques (BCTs), increased moderate-to-vigorous intensity PA (MVPA) and step counts after the intervention, and these changes were sustained 6 months after MBS. Thus, PA behavior change interventions seem promising to increase MVPA in the midterm and, in turn, limit weight regain to maintain health improvements. However, additional studies investigating the effects of behavior change interventions on MVPA are required owing to the heterogeneity and small number of studies available and the divergent results across studies with adults undergoing MBS [30].

Successful Behavior Change Interventions Targeting PA

Overview

Successful behavior change interventions are based on evidence and a good understanding of the targeted behavior and its correlates, context, and population [31,32]. Such interventions also require input from stakeholders, especially those who will receive it, which can be obtained via various methods. For example, to inform theory- and evidence-based decisions about the design and delivery of PA behavior change interventions, a web-based survey and focus groups were conducted with

adults undergoing MBS living in Quebec, Canada [33]. The results highlight 4 fundamental points to consider when developing a behavior change intervention to promote PA among adults undergoing MBS.

Needs Assessment and Patient Perspectives

First, the main PA motives before and after MBS include weight control, social support, pleasure, well-being, and physical fitness [34-40]. Therefore, PA interventions should identify strategies addressing these motives to meet patients' expectations and keep track of these for efficacy evaluations. Second, motivating adults to engage in PA, either before or after MBS, is challenging because of several barriers [41-44], including physical and psychological issues, such as pain, fatigue, weight, lack of motivation, and body dissatisfaction [34-40]. Other important PA barriers reported include perceived lack of time and resources, bad weather, and lack of social support [34-40], which can persist after MBS despite weight loss and health improvement [45]. In addition, new PA barriers may emerge after MBS caused by excess skin [46,47]. Accordingly, adults are likely to need support to overcome barriers to PA both before and after MBS. Ensuring that a well-trained PA counselor who can help intended users elucidate barriers and identify means to create an environment that makes PA easier and reduces barriers to action is important. Third, adults reported a preference for PA interventions starting 3 to 6 months before MBS and being offered continued support until 1 year after MBS [33], suggesting that initiating a PA behavior change intervention before MBS, with additional post-MBS follow-ups, may be most acceptable. Fourth, interventions offering face-to-face meetings with health professionals are preferable [33]. Accordingly, integration of supervision via regular meetings should thus be considered as a key element to enhance participants' adherence to the intervention and, in turn, their PA [48,49].

Multitheory Approach

Beyond the aforementioned considerations, it is necessary to draw on behavior change theories to target specific factors that influence PA behavior when developing PA behavior change interventions. Existing theories such as self-determination theory (SDT) [50] and social cognitive theory (SCT) [51] are 2 theories previously used in PA behavior change interventions [52], as they are especially relevant in identifying determinants of PA. SDT suggests that an individual's motivation to engage in a behavior, such as PA, is based on the satisfaction of their basic psychological needs of competence, autonomy, and relatedness [50]. From an SDT perspective, interventions can enhance needs satisfaction by providing autonomy support (ie, providing PA choices and minimizing perceived pressure) and structure (ie, communicating clear expectations, providing access to personalized information, and providing feedback) and by building strong interpersonal relationships with participants [50]. In turn, when an individual's needs are satisfied and their motivation to engage in a behavior is internalized and for self-determined reasons, because PA is enjoyable, pleasurable, of interest, and aligned with their values, their behavior is more likely to become habitual and maintained over time. Both quantitative and qualitative studies support these tenets [29,53,54]. SCT suggests that self-efficacy is a key determinant of PA [51]. From an SCT perspective, interventions fostering an individual's perceived self-efficacy via positive reinforcement can help promote PA uptake and adherence [55].

Using SDT and SCT when planning PA behavior change interventions, several studies have shown that targeting their underlying theoretical constructs (eg, perceptions of competence, autonomy and relatedness, motivational regulations, and self-efficacy) and introducing evidence-based motivational and behavior change techniques (MBCTs) can have a positive effect on PA outcomes [27,44,56]. MBCTs include shaping knowledge (ie, providing instruction on how to perform the behavior and how to monitor the behavior and affect), comparison of outcomes (ie, discussing pros and cons), natural consequences (ie, providing information about the health benefits of PA and monitoring of benefits or outcomes), goal setting (ie, setting goals, problem solving, action planning, discrepancy between current behavior and goal, review outcome goal or goals, behavioral contract, and commitment), fostering self-beliefs via verbal persuasion about the capability to overcome barriers, focus on past success, and self-talk, feedback, and monitoring (ie, providing feedback on behavior, self-monitoring of outcome or outcomes of behavior, and self-monitoring of behavior), associations (ie, picking prompts and cues), and rewards and threats (ie, building self-rewards) [27,44,56]. Collectively, studies have shown that a variety of SDT- and SCT-based interventions, including MBCTs, are promising for increasing PA in people with overweight or obesity [56,57]. However, no single theory has shown superiority in its ability to increase PA, and there is an increasing trend to include multiple MBCTs that map onto multiple theories to ensure that several key factors influencing PA are targeted [52,56]. As such, rather than choosing one theory, PA behavior change interventions including MBCTs related to SDT and SCT constructs should be considered, as they may increase the likelihood that patients awaiting MBS will initiate and maintain their PA.

Approaches to Delivering Interventions

PA behavior change interventions for adults with obesity include center-, community-, and home-based programs. However, alternative delivery formats, including email, phone, or videoconferencing counseling, have also been shown to be effective [58]. Videoconferencing counseling, otherwise referred to as telehealth interventions, have been introduced to address key issues and patients' preferences (eg, lack of time and resources, supervision, face-to-face, accessibility, and simplicity) while considering current contextual challenges (eg, limited financial and human resources, travel to and from MBS or research centers, pandemic lockdown, and environmental concerns) and maintaining opportunities for meetings with health professionals as per patient preferences. Therefore, it is important to develop and implement behavior change interventions using telehealth.

Telehealth refers to the use of the internet and connected technologies to provide care [59], and adherence rates as acceptability of such interventions are high (≥75%) [60-64]. The feasibility of telehealth interventions is very promising given the ubiquitous access to the internet and technologies in

Canada, with 94% of residents having access to the internet and 88% owning a smartphone [65]. Moreover, telehealth is cost-effective and has already been shown to improve health outcomes [60,62,66] and PA among adults with or without obesity [67,68]. Although many studies are available on telehealth interventions with patients who had undergone MBS [69-74], to our knowledge, only 3 of them included a PA behavior change intervention: 1 feasibility study before MBS (before-after study design) [72]; 1 feasibility study after MBS (before-after study design) [73]; and 1 ongoing randomized controlled study after MBS [74]. However, PA was generally self-reported and was only measured in the short term, introducing measurement bias and preventing the assessment of PA maintenance [71]. Robust and innovative study designs, such as a single-case experimental design with long-term objective PA measures, should be used in future studies to assess the effects of telehealth PA behavior change interventions in the short and long term. Therefore, Bari-Activ, having already shown its efficacy [22,28,29], was revised to reinforce theory-based content, reflect intended users' perspectives and the context in which the intervention will be conducted, and provide a means to increase reach (via telehealth). It will be tested within a single-case experimental design to ensure that it is feasible and applicable to intended users and implementers and generate data to inform a large-scale trial to test whether it is effective.

Objectives

This manuscript reports the protocol used in this study. The first objective is to assess the feasibility and acceptability of the protocol or methods and the Telehealth Bariatric Behavioral Intervention (TELE-BariACTIV), an intervention designed to increase MVPA that is guided by two perspectives: (1) a multitheory approach, thus targeting SDT and SCT constructs and integrating related MBCTs, and (2) a patient perspective. The second objective is to generate an estimate of the effect of the TELE-BariACTIV intervention on presurgical MVPA (the primary outcome for a future large-scale trial) to determine the appropriate sample size for a multicenter large-scale trial.

Methods

Study Design and Procedures

The study uses a phased approach to behavior change intervention development supported by the Obesity Related Behavioral Intervention Trials model [31].

The study results will be reported according to the recommendations for single-case protocols in behavioral interventions [75]. Owing to the objectives of the study (feasibility, acceptability, and effect size exploration) and recommendations [31,76], this study is a multicenter study with a single-case experimental design with multiple base levels (ABAB'A). It is an open-label trial in which research staff, researchers, and participants are not blinded to the study objectives, intervention, and allocation, given the nature of the intervention and measures.

Approximately 2 weeks before the baseline assessment, the study will be explained by phone to potential participants and the selection criteria, checked. Eligible and interested participants will be sent an accelerometer and a A370 Polar (Polar Electro) watch with cables to recharge and information sheet by mail with a prepaid return envelope. Participants will be instructed to initiate the baseline assessment on the web (Limesurvey) once they receive their packages, including an informed consent form. Then, participants will be randomly allocated to a 1- or 2-week baseline A1 phase using a list of random numbers generated electronically by a person outside the project, and they will start the 5 phases of the study (A1-B1-A2-B2-A3; Figure 1). The A phases are observational phases without intervention, and the B phases are intervention phases with PA counseling delivered via Zoom technology platform. Participants had different dates of starting the study owing to the variability in their MBS dates. Phase A2 may also vary in length because the exact MBS date is usually not known when participants are to start the study.

To meet the design standards that recommend at least 3 measurements per phase [75,77], MVPA is assessed continuously over 7 to 14 days during each phase. The storage limit of the accelerometer is 180 days, which ensures the feasibility of the measurement. Therefore, participants have to download the free Actisync application on a computer, connect the device with a cable, and then upload their anonymized accelerometry data using the Actigraph Centerpoint minimum every 180 days. Quality of life, anxiety and depressive symptoms, motivational regulations, basic psychological needs satisfaction and frustration, self-efficacy to overcome barriers to PA, PA enjoyment, and social support for exercise are assessed using a series of validated questionnaires 6 to 10 times via Limesurvey (Table 1). In addition, participants are asked to respond to questions regarding the acceptability of the protocol and intervention in web-based questionnaires before and after the intervention (phase B1), as well as during a web-based semistructured individual interview 1 to 4 weeks after phase B1. Medical records will be consulted at the end of the study with the participants' authorization to validate the MBS date, medical conditions, and weight loss.

Figure 1. Study design.

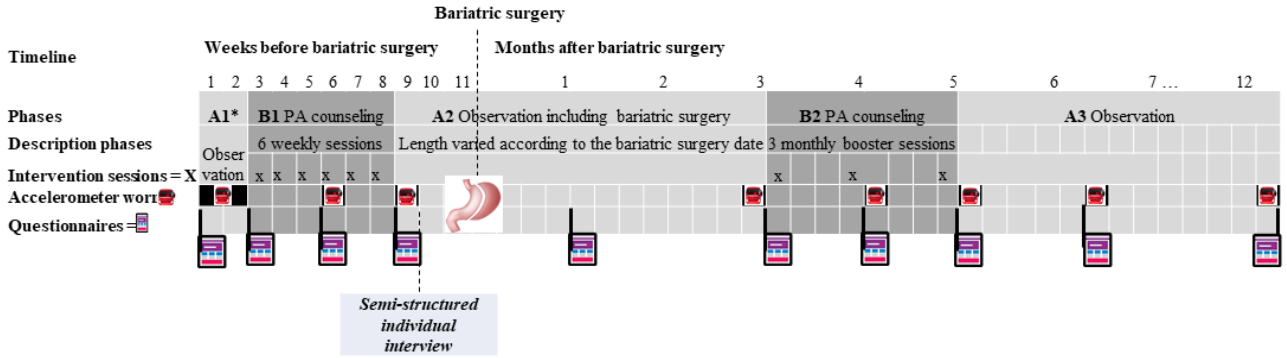

Table 1. Description of the assessment of the study outcomes, all completed in French.

Outcomes	Assessment methods and tools	Number of assessments and timing
Primary outcomes		
Feasibility	• Refusal, recruitment, retention, attendance, attrition, and missing data rates tracking by study staff	• Throughout the study
Acceptability	• Technical Quality Assessment Questionnaire • Semistructured individual interviews • Acceptability questionnaire developed by the study authors	• 9; immediately after each intervention session during phases B1 and B2 • 1; 1 to 4 weeks after phase B1 • 2; 1 to 3 days before and after phase B1
Secondary outcomes		
Behavior targeted: MVPA[a] (primary outcome for a future large-scale trial)		
MVPA (min/days)	• Accelerometer (Actigraph)	• 8; during the 7 or 14 days of the phase A1, during 7 days before phase B2, mid- and after phases B1 and B2, as well as 6 and 12 months after MBS[b] (phase A3)
Generalization measures (secondary outcomes for future large-scale trial)		
Health-related quality of life	• RAND 36-item health survey	• 10; 1 to 3 days before phase A1, 1 to 3 days before, mid- and after phases B1 and B2, as well as 1, 6, and 12 months after MBS (phase A3)
Anxiety and depressive symptoms	• PHQ-9[c] • GAD-7[d]	• 10; 1 to 3 days before phase A1, 1 to 3 days before, mid- and after phases B1 and B2, as well as 1, 6, and 12 months after MBS (phase A3)
Motivational regulations for PA[e]	• BREQ2[f]	• 6; 1 to 3 days before and after each phase
Basic psychological needs satisfaction and frustration	• BPNSFS[g]	• 6; 1 to 3 days before and after each phase
Self-efficacy for PA	• Self-efficacity scale to overcome PA barriers developed by the study authors following Bandura's recommendations	• 6; 1 to 3 days before and after each phase
PA enjoyment	• PACES[h]	• 6; 1 to 3 days before and after each phase
Social support for exercise	• SSES[i]	• 6; 1 to 3 days before and after each phase
Covariables		
Sociodemographic data	• Questionnaire developed by the study authors	• 1; 1 to 3 days before phase A1
Smoking status	• Self-reported	• 6; 1 to 3 days before and after each phase
Alcohol consumption	• AUDIT-C[j]	• 6; 1 to 3 days before and after each phase
BMI and weight loss	• Self-reported medical records	• 6; 1 to 3 days before and after each phase
Medications and medical conditions	• Medical records	• 6; 1 to 3 days before and after each phase
Date and place of MBS	• Self-reported medical records	• 1; at the end of the study
Pain	• RAND 36-item health survey (bodily pain subscale)	• 10; 1 to 3 days before phase A1, 1 to 3 days before, mid- and after phases B1 and B2, as well as 1, 6, and 12 months after MBS (phase A3)

Outcomes	Assessment methods and tools	Number of assessments and timing
Sedentary time, time spent on light-intensity PA, and step count	• Accelerometer (Actigraph) • GPAQ[k]	• 8; during the 7 or 14 days of the phase A1, during 7 days before phase B2, mid- and after phases B1 and B2, as well as 6 and 12 months after MBS (phase A3) • 10; 1 to 3 days before phase A1, 1 to 3 days before, mid- and after phases B1 and B2, as well as 1, 6, and 12 months after MBS (phase A3)
Self-reported sitting time and MVPA (min/week)	• Accelerometer (Actigraph) • GPAQ	• 8; during the 7 or 14 days of the phase A1, during 7 days before phase B2, mid- and after phases B1 and B2, as well as 6 and 12 months after MBS (phase A3) • 10; 1 to 3 days before phase A1, 1 to 3 days before, mid- and after phases B1 and B2, as well as 1, 6, and 12 months after MBS (phase A3)

[a]MVPA: moderate-to-vigorous intensity physical activity.

[b]MBS: metabolic and bariatric surgery.

[c]PHQ-9: Patient Health Questionnaire.

[d]GAD-7: Generalized Anxiety Disorder scale.

[e]PA: physical activity.

[f]BREQ-2: Behavioral Regulation in Exercise Questionnaire-2.

[g]BPNSFS: Basic Psychological Need Satisfaction and Frustration Scale.

[h]PACES: Physical Activity Enjoyment Scale.

[i]SSES: Social Support for Exercise Survey.

[j]AUDIT-C: alcohol use disorder identification test–concise.

[k]GPAQ: Global Physical Activity Questionnaire.

Participants

Participants are adults residing in or around 3 cities (ie, Montreal, Quebec City, and Chicoutimi) in the province of Quebec (Canada) and receiving care at either one of 2 tertiary care centers (Institut Universitaire de Cardiologie et de Pneumologie de Québec-Université Laval and the Centre Intégré Universitaire de Soins et de Services de Santé [CIUSSS] du Nord-de-l'Île-de-Montréal) or at a regional center (CIUSSS du Saguenay–Lac-Saint-Jean). Recruited strategies include (1) placing posters in waiting rooms at the target centers and (2) asking health professionals from hospitals at each site to refer to potentially eligible patients. For the latter, health professionals will provide the research team with the name and contact information of patients who have a planned sleeve gastrectomy in >12 weeks and who have provided verbal consent to be contacted by the research team for information on the study. The target sample size will be 12 (approximately 4 per site), which is considered acceptable for a single-case experimental study with multiple base levels, as participants serve as their own control, and outcomes will be measured repeatedly across observational and interventional phases [75,77].

The inclusion criteria are (1) ≥18 years of age; (2) scheduled to undergo sleeve gastrectomy in >12 weeks in one of the 3 associated hospitals (University Institute of Cardiology and Pulmonology of Quebec, Quebec; Sacré Cœur Hospital, Montreal [CIUSSS du Nord-de-l'Île-de-Montréal]; Chicoutimi Hospital, Chicoutimi [CIUSSS Saguenay–Lac-Saint-Jean]) Qc, Canada); (3) self-report ≤150 minutes of MVPA per week; and (4) access to a computer with internet and an interface with a camera. Exclusion criteria are (1) having a contraindication to PA without medical clearance (the Get Active questionnaire from the Canadian Society for Exercise Physiology [78] is used to determine if medical clearance is needed); (2) already enrolled in a supervised exercise intervention or PA behavior change intervention; (3) inability to speak and understand French; and (4) need a wheelchair, cane, walker, or other support or supports to move.

Measurements

Primary Outcomes

Feasibility

The feasibility of the protocol or methods will be assessed at the end of the study using the following criteria tracked by the study staff: (1) refusal rate (percentage of participants who declined to participate); (2) recruitment rate (number of participants recruited per month at each center, number of sleeve gastrectomies performed per month at each center during the recruitment period), and sources of referral (eg, professionals, and self via poster); (3) retention rate (percentage of participants who complete all assessments and interviews); and (4) percentage of missing data (overall or total, per participant, per outcome, and per assessment time point). The feasibility of the intervention will be assessed at the end of the study using the following data tracked by the study staff: (5) attendance rate (number of sessions completed by participants) and (6) attrition rate (percentage of participants who did not complete the

intervention). In addition, the reasons for refusing to participate in the study, as well as the reasons for dropping out of the study and the intervention, are documented by study staff, when available, and will be reported at the end of the study.

Acceptability

Immediately after each intervention session, the PA counselor completes the technical quality assessment questionnaire to report their satisfaction with the quality and performance of the Zoom technology platform [79]. The questionnaire includes 5 items: the first 3 concern the technological difficulties encountered by the PA counselor, and the last 2 relate to audio and video difficulties experienced by the participant. A high score indicates a low occurrence of technical problems. The questionnaire is modified for the study by adding 3 questions to assess the PA counselor's perceived quality of the relationship with the participant, whether they believed the intervention session goals were met, and their overall satisfaction with the intervention session, with response options ranging from 0 to 10 (from lowest to highest satisfaction rate).

The acceptability of the protocol or methods and intervention is assessed during semistructured individual interviews with participants conducted via the Zoom platform. Participants are asked about their perceptions, opinions, and experiences regarding the intervention and study protocol or methods (eg, positive and negative experiences, adverse events related to the intervention and study, barriers, facilitators, satisfaction, perceived benefits, and suggestions for improvement). In addition, participants complete a 7-item questionnaire with statements in the future tense for before phase B1 or past tense for after phase B1, developed by the study authors (Arbour, G, unpublished data, July 2022), with items covering the 7 concepts of the *Theoretical Framework of Acceptability* by Sekhon et al [80] (ie, affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy).

Secondary Outcomes

MVPA (Primary Outcome for the Future Large-scale Trial)

Daily MVPA is directly assessed using a triaxial accelerometer worn at the hip on the right side (Actigraph wGT3X-BT) during phase A1 and then for 7 days during the other assessment time points (Figure 1). Participants are instructed to wear the accelerometer continuously, except during water-based activities, and to maintain a log of wear times with waking and bed times. Accelerometer data will be extracted and downloaded (10-second epochs) using Actilife version 6.13.4 and will be cleaned in accordance with the logbooks provided by the participants. Only data from participants who wear the accelerometer for ≥3 days (including at least 1 weekday and 1 weekend day) and ≥10 hours/day will be analyzed [18,81]. The nonwear time is defined as a period of ≥120 minutes of consecutive zeros [82]. Accelerometer data will be used to quantify the time spent in MVPA (min/day). As PA intensity classifications have not yet been established for adults undergoing MBS, existing threshold values for the general population will be used for analyses (moderate-intensity PA=1952-5724 and vigorous-intensity PA 5724 counts/min) [83].

Data gathered immediately after phase B1 will be used to estimate effect sizes to determine sample size calculation for a future large-scale trial. Achieving PA recommendations of ≥150 min/week of MVPA will be judged as clinically significant [84,85].

Generalization Measures (Secondary Outcomes for the Future Large-scale Trial)

As recommended in the study by Tate et al [75], generalization measures are administered to increase the external validity of the study [86]. Generalization measures are dependent variables measured in addition to the targeted behavior to assess whether the effects of the intervention will be generalized to other results in the scientific literature [87]. In this study, generalization measures are used to assess changes in several psychosocial factors related to PA, spanning SDT, SCT, and health.

Health-related quality of life is assessed using the generic *RAND*-36 questionnaire [88], a 36-item questionnaire evaluating 8 concepts: physical functioning, role limitations owing to physical health, role limitations owing to emotional problems, energy or fatigue, emotional well-being, social functioning, pain, and general health perceptions. In addition, the *RAND*-36 contains an additional item to assess the perceived change in health status. The overall physical and mental health scores will be calculated from the 8 subscales [88]. A 3- to 5-point increase in overall physical and mental health scores is considered clinically significant [89,90]. According to the literature, owing to the likely absence of weight loss associated with the pre-MBS intervention, a score of 3 will be used as the minimal clinically important difference (MCID) [28,91].

The severity of anxiety and depressive symptoms will be assessed using the Patient Health Questionnaire (PHQ-9) [92] and the Generalized Anxiety Disorder scale (GAD-7) [93] as recommended by Obesity Canada [8]. The PHQ-9 is a 9-item validated scale that assesses the intensity of depressive symptoms. The GAD-7 is a 7-item self-rating scale that assesses the severity of anxiety symptoms. The MCID for the PHQ-9 and GAD-7 [94], based on the range of baseline depressive or anxiety symptom severity, will be used. Then, the MCID range will be 0 to 10 points (10/21, 48%) on the GAD–7 and 0 to 14 points (14/27, 52%) on the PHQ-9 for participants with baseline very mild to high anxiety or depression symptoms [94].

Theoretical Construct Measures (Secondary Outcomes for the Future Large-scale Trial)

To explore whether the intervention can change one or several of the theoretical constructs targeted, several measures are used to assess SDT, SCT, and evidence-based PA determinants [54,95,96], including PA enjoyment, motivational regulations for PA, psychological needs satisfaction and frustration, self-efficacy to overcome barriers to PA, and social support for exercise. PA enjoyment is assessed using the 18-item PA Enjoyment Scale [97]; motivational regulations for PA (ie, intrinsic, identified, introjected, integrated, external, and amotivation) are assessed using the 19-item Behavioral Regulation in Exercise Questionnaire-2 [95]; basic psychological

needs satisfaction and frustration (ie, perceptions of autonomy, relatedness, and competence satisfaction and frustration) are assessed using the 24-item Basic Psychological Need Satisfaction and Frustration Scale [98,99]; self-efficacy to overcome common barriers to PA is assessed using a 20-item questionnaire developed by the research team according to Bandura's recommendations. Participants are asked about their confidence to engage in PA 3 times per week in the presence of 20 different types of conditions using a 0% ("not confident at all") to 100% ("highly confident") scale [100], and perceived social support for PA received from family and friends is assessed using the 26-item Social Support for Exercise Scale [101,102]. Each measure will be scored following the scoring procedures, wherein higher scores will reflect greater PA enjoyment, intrinsic, identified, introjected, integrated, external, amotivation, self-efficacy to overcome common barriers to PA, psychological needs satisfaction, psychological needs frustration, and perceptions of social support for exercise.

Covariables

A questionnaire created by the authors is used to gather sociodemographic (age, sex, level of education, marital and professional status, number of children, and income) and clinical data (MBS date, medical conditions, and weight). The accuracy of the self-reported clinical data will be verified at the end of the study by reviewing the participants' medical records. Smoking status (nonsmoker, smoker, or former smoker) is self-reported, and unhealthy alcohol consumption is assessed using the Alcohol Use Disorder Identification Test-Concise [103].

Sedentary time (hours/day), light PA (min/week), and daily step count is assessed using accelerometers with the following threshold values used for analyses: sedentary time ≤100 counts/min, light-intensity PA=100-1951 min/week [83]. The Global Physical Activity Questionnaire [104] is also completed by the participants to obtain self-reported PA data because it allows for the estimation of participants' levels of PA during previous 7 days in 3 domains (work, travel to and from places, and recreational activities), which is not possible with accelerometers [104]. Total self-reported MVPA (min/week) will be calculated by summing the MVPA scores for transportation, leisure, and work. The question— "How much time do you usually spend sitting or reclining on a typical day?"—in the Global Physical Activity Questionnaire will be used to assess self-reported sedentary time.

Pain is assessed using the *RAND*-36 Physical Pain subscale, which consists of the following two validated items: (1) How much bodily pain have you had during the past 4 weeks? (2) During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? An average score will be computed, whereby higher levels will reflect greater pain levels.

The TELE-BariACTIV Intervention

During phase B1, participants will receive 6 real-time, face-to-face sessions with the same PA counselor (to the extent possible) over a 6-week period before MBS. The sessions will last approximately 45 minutes and will be conducted via videoconferencing using Zoom. The TELE-BariACTIV intervention is a multicomponent intervention derived from a previous intervention by Bond et al [22,28,29], which was developed based on multiple theories, including SDT and SCT, and was revised by the current research team. The intervention targets SDT and SCT constructs, focusing specifically on (1) providing autonomy support, structure, and interpersonal involvement; (2) increasing perceptions of autonomy (ie, perceived control over one's actions by providing a rationale, structure, and emphasizing responsibility), competence (ie, perceived mastery of tasks and skills by providing support and encouragement, information feedback, and support barrier identification), and relatedness (ie, perceived belonging and connection to others by encouraging to seek social support); (3) increasing autonomous motivation for PA (ie, acting through self-endorsement and volition because the activity holds inherent interest or personal value); and (4) fostering perceived self-efficacy to overcome PA barriers and engage in PA. Accordingly, the intervention integrates several content- and relational-based techniques hypothesized to target the theoretical constructs. The techniques are selected on the basis of the theoretical construct or constructs they are proposed to target, wherein the research team drew on published literature [105-108] to determine which techniques target specific SDT and SCT constructs to guide the selection. The MBCTs used to guide the content of the intervention sessions during phase B1 are presented in Table 2.

In addition, the PA counselor uses motivational interviewing techniques [108] (ie, empathic or reflective listening, asking open-ended questions, prompting the participant to ask questions, prompting participants to offer solutions, seeking permission to provide information and advice, shifting focus, supporting change or persistence, and showing unconditional regard) that align with SDT and SCT for the relational component of the intervention to support the delivery of the content. The goal of the intervention is to address participants' mindset about PA, as well as their motivation to engage in PA, with the goal of supporting PA uptake and maintenance. To this end, participants are encouraged to progressively increase their daily PA to achieve the current PA guidelines of 150 minutes per week of MVPA by the end of phase B1 (before MBS) and to maintain or increase PA levels during phases B2 (after MBS) and A3 (at the 1-year follow-up). Owing to the goal of helping participants increase and maintain PA after MBS, participants are offered 3 booster sessions to discuss progress or relapses and work on PA psychosocial and cognitive processes already addressed during phase B1. These sessions are one-on-one sessions, occur at 1-month intervals, and are conducted via videoconferencing using Zoom. They last 45 minutes, though they can be shorter as the topics are not pre-established; rather, the participants are free to choose the topics according to their needs. Length and topics discussed are recorded by the PA counselor.

Table 2. Overview of the telehealth bariatric behavior intervention[a].

Session number and overview	Topics	Content- and relation-based techniques (motivation and behavior change techniques, and motivational interviewing techniques)
1. Welcome to the trial	• Discuss importance of PA[b] within context of bariatric surgery • Identify health risks of a sedentary lifestyle and health benefits of an active lifestyle • Evaluate perceived benefits and personal barriers related to PA adoption • Establish baseline daily average PA minutes and steps • Discuss PA target • Provide PA monitoring logbook, pedometer, and instructions for recording daily bout-related walking exercise minutes and steps • Provide information about the benefits and costs of action or inaction to participants	• Review specific guidelines for PA participation • Discuss benefits of PA and elicit participants' reasons for increasing PA • Examine cost and benefit of current PA behavior and changing behavior • Acknowledge any internal conflict regarding PA adoption • Offer clear rationale for PA adoption • Self–re-evaluation (explore congruence between values, goals, and lifestyle) • Assess motivational readiness • *Shaping knowledge*: Instruction on how to perform the behavior, and how to monitor behavior and affect • *Comparison of outcomes*: Credible source, pros and cons • *Natural consequences*: Information about health consequences
2. Goal setting for behavior resolution	• Introduce goal-setting principles, set goals targeting behaviors to increase PA • Identify pleasant or unpleasant aspects of PA • Differentiate extrinsic and intrinsic motives and rewards • Identify ways to make PA more enjoyable	• Review SMART[c] goal approach • Facilitate short- and long-term goal development • Emphasize enjoyable aspects of PA • *Goal setting*: Goal setting, problem solving, action planning, discrepancy between current behavior and goal, review outcome goal or goals, behavior contract, and commitment • *Self-belief*: Verbal persuasion about capability, focus on past success, and self-talk • *Natural consequences*: Information about health consequences, salience of consequences, monitoring of emotional consequences, and anticipated regret • *Scheduled consequences*: Reward alternative behavior
3. Building a preoperative PA program	• Differentiate lifestyle and structured PA • Brainstorm ways to increase lifestyle PA • Teach talk test to gauge PA intensity • Discuss making PA a habit • Record of PA behavior • Record of outcomes related to PA • Instruction to perform behavior • Prompt practice	• Review methods of self-monitoring • Encourage the use of a self-monitoring technique to evaluate progress postintervention • *Goal setting*: Goal setting, problem solving, action planning, discrepancy between current behavior and goal, review outcome goal or goals, behavior contract, and commitment • *Feedback and monitoring*: Feedback on behavior, self-monitoring of outcome or outcomes of behavior, self-monitoring of behavior • *Self-belief*: Verbal persuasion about capability, focus on past success, and self-talk • *Reward and threat*: Self-reward • *Associations*: Prompts or cues
4. Creating an active environment: Making physical and social cues work for you	• Environmental restructuring • Identify positive environmental cues to increase PA • Provide information on where and when to perform PA • Identify strategies to eliminate or avoid inactivity cues • Plan social support or social change	• Review main types of social support • Encourage participants to examine social network • Develop reasons and plans to include others in their lifestyle changes • Have participants examine their current environment and determine methods for creating a PA-promoting environment • *Goal setting*: Goal setting, problem solving, action planning, discrepancy between current behavior and goal, review outcome goal or goals, behavior contract, and commitment • *Feedback and monitoring*: Feedback on behavior, self-monitoring of outcome or outcomes of behavior, and self-monitoring of behavior • *Antecedents*: Restructuring the physical environment, restructuring the social environment, and body changes • *Social support*: Social support (unspecified), social support (practical), and social support (emotional)

Session number and overview	Topics	Content- and relation-based techniques (motivation and behavior change techniques, and motivational interviewing techniques)
5. Resolving issues and planning	• Problem-solving • Action planning • Barrier identification or problem solving • Increasing self-efficacy	• Elicit potential barriers that participants may experience • Develop plans to overcome barriers • *Goal setting*: Goal setting, problem solving, action planning, discrepancy between current behavior and goal, review outcome goal or goals, behavior contract, and commitment • *Feedback and monitoring*: Feedback on behavior, self-monitoring of outcome outcomes of behavior, and self-monitoring of behavior • *Self-belief*: Verbal persuasion about capability, focus on past success, self-talk • *Repetition and substitution*: Behavior substitution
6. Putting it all together and establishing commitment or habit	• Develop new contract to facilitate commitment to maintenance of PA change consisting of short-, medium-, and long-term goals • Relapse prevention or coping planning	• Behavior contracting or self-liberation • Social support or helping relationships • Self–re-evaluation • Mastery experiences • *Goal setting*: Goal setting, problem solving, action planning, discrepancy between current behavior and goal, review outcome goal or goals, behavior contract, and commitment • *Self-belief*: Verbal persuasion about capability, focus on past success, and self-talk • *Feedback and monitoring*: Feedback on behavior, self-monitoring of outcome or outcomes of behavior, and self-monitoring of behavior • *Antecedents*: Restructuring the physical environment, restructuring the social environment, and body changes • *Social support*: Social support (unspecified), social support (practical), and social support (emotional) • *Repetition and substitution*: Habit formation • *Associations*: Prompts or cues

[a]Behavior change technique groupings refer to the hierarchically clustered 93 techniques presented in the behavior change technique taxonomy (v1), are italicized, and specific techniques to be used follow the colons.

[b]PA: physical activity.

[c]SMART: specific, measurable, attainable, relevant, time-based.

In addition, participants are encouraged to use the provided PA monitor (A370 Polar watch) for the study duration to track their PA behavior (not for research data collection), as this has been shown to be an effective way to increase goal setting, self-monitoring, and overall PA adherence [109,110].

PA counselors are persons with at least a bachelor's degree in kinesiology or a related field (eg, nursing care and physiotherapy). They receive training and supervision from AB and JB. As part of their training, they are required to participate in a 2-hour training course facilitated by JB, AB, and Jenson Price on how to deliver the intervention. In addition, they are observed performing the mock counseling encounters and take part in a bracketing interview with JP to reflect on their own background, perceptions, and interests and to explore how these could impact them in their role. PA counselors also receive an intervention manual created by JB, AB, and JP and reviewed by PB, AJR, and DB, which details the intervention. Specifically, the manual provides session plans and suggested activities, as well as relevant worksheets and documents that are shared with participants via mail and email. Finally, notes for each session with duration, topics discussed, accomplishment of session objectives, participants' reactions to the content, next steps with the participants, and reflection as a PA counselor (eg, problems arising during the sessions, overall experience delivering the session, suggestion for intervention or personal improvements, and session deviations) are taken by the PA counselor using a standardized form and discussed with AB, if needed. This information will be used to track fidelity to the intervention protocol and explore avenues for intervention improvement in future large-scale trials.

Internal Validity

During the individual interviews, the participants are asked about all life events or factors that occurred during the study period (eg, divorce, injuries, illness, lockdown, and new employment) that may have impacted the study results. This strategy allows for greater certainty in confirming whether any changes observed are related to the intervention [111].

Statistical Analyses

Descriptive statistics will be computed for baseline sociodemographic, clinical, feasibility, and acceptability data derived from the numerical responses and close-ended questions.

All statistical analyses will be carried out using R and the following packages: scan, SCRT [112], metafor, ggplot2, and tydiverse. For the primary outcomes of a future large-scale trial, a comparison of daily MVPA based on accelerometer data between phases A1 and B1 will be carried out using a randomization test for a single-case experimental design [113]

for each participant. Subsequently, individual effect sizes will be aggregated in a meta-analysis to obtain a group-based effect size. This will provide the necessary information for computing the required sample size for a future large-scale trial. A sensitivity analysis will also be performed to compare A1 and B1 using a Tau-*U* test [114]. Then, a second meta-analysis will be performed using the same approach. The global effect of the intervention on daily MVPA will be tested using another set of randomization tests comparing the ABABA phases. This test makes it possible to compare 2 short time series and to provide an effect size in case of a significant difference. This analysis will be performed on an individual scale.

Generalization measures (secondary outcomes for a future large-scale trial: health-related quality of life, anxiety, and depression symptoms) will be analyzed using the Reliable Change Index or cutoff score for descriptive purposes; the differences in individual scores across phases will be compared [115].

Theoretical construct measures (secondary outcomes for a future large-scale trial: PA enjoyment, motivational regulations for PA, basic psychological needs satisfaction and frustration, self-efficacy to overcome PA barriers, and social support for exercise) and self-reported MVPA will be analyzed using visual analysis. As recommended [116], stability, mean level change, and range of data by phase will be examined.

Content analysis of participants' responses to open-ended questions during the interviews and of the PA counselors' notes completed after the session will be conducted to identify themes and see if or what changes to the protocol or methods or intervention are warranted [117]. This will involve five steps, which will be followed by 2 research staff members: (1) familiarize themselves with the data by reading each transcribed interview several times before coding and looking for patterns, (2) code the transcripts and compile the initial codes, (3) put together similar codes to form potential themes and subthemes, (4) review the main themes and subthemes in relation to the data, and (5) define and name themes, select illustrative quotes from the interviews and produce a report.

Ethics Approval

The study protocol was approved by the Institutional Review Boards at the CIUSSS du Saguenay–Lac-Saint-Jean (approval MP-25-2021-354; 2021-6-11), the Institut Universitaire de Cardiologie et de Pneumologie de Québec-Université Laval (approval MP-25-2021-354; 2021-8-2), and the CIUSSS du Nord-de-l'Île-de-Montréal (approval MEO-25-2022-2264; 2021-10-22).

Results

The study began in September 2021, and as of July 2022, 12 participants have provided informed consent and been enrolled. Data collection is expected to end in fall 2023, depending on the MBS date. Analysis of pre-MBS data is planned for fall 2022, with the manuscript expected to be submitted in spring 2023. Analysis of post-MBS data is planned for fall 2023, with a second manuscript expected to be submitted in spring 2024.

The achievement of the following criteria based on the literature [22,28,29,63,72,73,118] will be considered satisfactory: (1) refusal rate ≤20%, (2) recruitment rate ≥1.8 participants recruited per month, (3) retention rate after phase B1 (before MBS) ≥80%, (4) percentage of missing data after phase B1 (before MBS) ≤10%, (5) intervention attendance rate ≥80%, and (6) intervention attrition rate ≤20%.

Discussion

Principal Findings

Increasing MVPA uptake and maintenance in adults undergoing MBS is a public health priority. This study will provide critical evidence pertaining to the feasibility and acceptability of the TELE-BariACTIV aimed at promoting MVPA before and after MBS while addressing several barriers to MVPA and intervention engagement previously identified, as well as the protocol or methods proposed to evaluate it. The data collected in the individual interviews will help optimize the intervention and protocol or methods for a larger study. In addition, an estimate of the effect of the TELE-BariACTIV intervention on MVPA will be useful for calculating the required sample size for future multicenter large-scale trials.

This paper describes the protocol and intervention used in the TELE-BariACTIV study. To our knowledge, only 2 studies investigating PA behavior change interventions among adults undergoing MBS have been published [72,73]. The TELE-BariACTIV study extends these previous works by prolonging the duration of the intervention (to cover both before and after MBS) and accordingly integrates longer follow-up assessments to assess initial changes in PA and maintenance of PA. Furthermore, the intervention and protocol or methods were designed to be as accessible and simple as possible (ie, distance-based), with no need for in-person assessments or intervention sessions while still using an objective PA measure.

A single-case experimental study with multiple base levels (ABAB'A) design, in which a small group of participants is used to test causal relationships between variables of interest, is often used in behavior research because it allows rigorous experimental manipulation of independent variables and repeated measures of dependent variables over time [119]. This design has been used with various clinical populations to study different behaviors, including PA [87,120,121] in patients who have undergone MBS [122]. In addition, observational phases improve internal validity by controlling for maturation and historical variables, thus performing a function similar to that of the control group without intervention [75].

Limitations

Although the TELE-BariACTIV intervention was developed according to patients' preferences, some patients will like other options (eg, in-person intervention and supervised exercise training), and some will be excluded because they have no internet access or interface with a camera and need supportive devices to move, leading to potential enrollment difficulties and selection bias. The feasibility of the intervention in the general MBS population will not be assessed. However, this could be the goal of another larger study. In addition, recruitment began

during the COVID-19 pandemic period. The COVID-19 pandemic has led to an overload on the health care system, which presumably slowed recruitment. Thus, the recruitment rate that will be estimated after the study is likely to be conservative. MBCTs are grouped together, so there is no way to know which technique has more or less impact on MVPA change. Nevertheless, the main aim of this initial study is to explore the effect of the intervention to calculate the sample size for a future large-scale trial and not to isolate the most efficacious intervention components. Finally, several outcome measures used are not specific to patients who have undergone MBS and may not be sensitive enough to capture slight changes that may be clinically meaningful for this population. Therefore, participants are offered an opportunity to share any additional thoughts they have, which can relate to any change in the outcomes measured during the interview.

To conclude, the TELE-BariACTIV study is innovative in its approach and design [76]. Feasibility and acceptability evidence would support proceeding with a larger trial that is sufficiently powered to test its effectiveness. Moreover, the TELE-BariACTIV intervention has strong potential for sustainability in the current context (pandemic, environmental, and budgetary restrictions). Indeed, given the ubiquity of the internet, TELE-BariACTIV intervention could be implemented across Canada to support cost-effective efforts to promote PA in this growing, mostly inactive, segment of the population. In addition, it would offer adults access to supportive care and trained professionals regardless of where they live. Finally, use of distance-based means to collect data to encourage participation of adults near and far from urban centers and use of technology to deliver the intervention to address participants' lack of time and unwillingness to travel for in-person sessions are strengths of this study.

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Data Availability

Data generated or analyzed during the study will be included in the published article and its supplementary information files. Additional information will be available from the corresponding author upon request.

Authors' Contributions

AB, MSP, PB, AJR, PYG, LB, AT, PB, MFL, and JB conceptualized and designed the study. AB, PB, AJR, DB, and JB made substantial contributions to the conception and design of the intervention. AB and JB conceived and designed the intervention manual with assistance of JP. AB, JL, MSP, JB, and PB wrote the manuscript. All the authors critically revised the manuscript and approved the final manuscript.

Conflicts of Interest

AT and LB received funding from Johnson & Johnson, Medtronic, and GI Windows for studies on bariatric surgery; AT has been a consultant for Biotwin, Bausch Health, Novo Nordisk, and Eli Lilly; MFL has been a consultant for Eli Lilly, Novo Nordisk, and Takeda; and research funding from Merck Canada and Novo Nordisk.

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Abbreviations

CIUSSS: Centre Intégré Universitaire de Soins et de Services de Santé
GAD-7: Generalized Anxiety Disorder scale
MBCT: motivational and behavior change technique
MBS: metabolic and bariatric surgery
MCID: minimal clinically important difference
MVPA: moderate to vigorous intensity physical activity
PA: physical activity
PHQ-9: Patient Health Questionnaire
SCT: social cognitive theory
SDT: self-determination theory
TELE-BariACTIV: Telehealth Bariatric Behavioral Intervention

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Protocol

Generation of Cascades of Care for Diabetes and Hypertension Care Continuum in Cambodia: Protocol for a Population-Based Survey Protocol

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Abstract

Background: Cardiovascular diseases (CVDs) were accountable for 24% of the total deaths in Cambodia, one of the low- and middle-income countries, where primary health care (PHC) settings generally do not perform well in the early detection, diagnosis, and monitoring of leading risk factors for CVDs, that is, type 2 diabetes (T2D) and hypertension (HT). Integrated care for T2D and HT in the Cambodian PHC system remains limited, with more than two-thirds of the population never having had their blood glucose measured and more than half of the population with T2D having not received treatment, with only few of them achieving recommended treatment targets. With regard to care for T2D and HT in the public health care system, 3 care models are being scaled up, including (1) a hospital-based model, (2) a health center–based model, and (3) a community-based model. These 3 care models are implemented in isolation with relatively little interaction between each other. The question arises as to what extent the 3 care models have performed in providing care to patients with T2D or HT or both in Cambodia.

Objective: This protocol aims to show how to use primary data from a population-based survey to generate data for the cascades of care to assess the continuum of care for T2D and HT across different care models.

Methods: We adapt the HIV test-treat-retain cascade of care to assess the continuum of care for patients living with T2D and HT. The cascade-of-care approach outlines the sequential steps in long-term care: testing, diagnosis, linkage with care, retention in care, adherence to treatment, and reaching treatment targets. Five operational districts (ODs) in different provinces will be purposefully selected out of 103 ODs across the country. The population-based survey will follow a multistage stratified random cluster sampling, with expected recruitment of 5280 eligible individuals aged 40 and over as the total sample size. Data collection process will follow the STEPS (STEPwise approach to NCD risk factor surveillance) survey approach, with modification of the sequence of the steps to adapt the data collection to the study context. Data collection involves 3 main steps: (1) structured interviews with questionnaires, (2) anthropometric measurements, and (3) biochemical measurements.

Results: As of December 2021, the recruitment process was completed, with 5072 eligible individuals participating in the data collection; however, data analysis is pending. Results are expected to be fully available in mid-2022.

Conclusions: The cascade of care will allow us to identify leakages in the system as well as the unmet need for care. Identifying gaps in the health system is vital to improve efficiency and effectiveness of its performance. This study protocol and its expected results will help implementers and policy makers to assess scale-up and adapt strategies for T2D and HT care in Cambodia.

Trial Registration: International Standard Randomised Controlled Trials Number (ISRCTN) registry ISRCTN41932064; https://www.isrctn.com/ISRCTN41932064

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KEYWORDS

diabetes; hypertension; cascade of care; implementation research; care models; population-based survey; continuum of care

Introduction

Globally, cardiovascular diseases (CVDs) are responsible for the death of 17.9 million people annually, accounting for 31% of all deaths [1]. More than 75% of deaths attributable to CVDs occur in low- and middle-income countries (LMICs), where primary health care (PHC) settings generally do not perform well in the early detection, diagnosis, and monitoring of type 2 diabetes (T2D) and hypertension (HT), which are the leading risk factors for CVDs [1,2]. In regions where early diagnosis and care are not available or inadequate, T2D and HT-related complications—including CVDs, kidney disease, neuropathy, blindness, and lower-extremity amputation—are a significant cause of morbidity and mortality among people with T2D or HT or both [3,4]. The resulting complications will increase health care costs and pose challenges to population health, socioeconomic development, and health systems [5,6], negatively affecting country's effort to achieve universal health coverage [7]. Globally, adult populations with HT and T2D had increased from 594 million to 1.13 billion between 1975 and 2015 [8] and from 4.7% to 8.5% between 1980 and 2014 (with approximately 422 million living with T2D in 2014), respectively [2]. Access to a lifelong continuum of care is therefore critical for those living with T2D or HT or both as well as for the prevention of CVDs [9]. The World Health Organization Package of Essential Noncommunicable Disease Interventions (WHO PEN) offers substantial international support for PHC services to include care for T2D and HT in LMICs [10].

In Cambodia, CVDs were estimated to account for 24% of the total deaths in 2018 [11], and in 2016 the prevalence rates of T2D and HT were 9.6% and 14.2%, respectively, among adult population between the ages of 18 and 69 years [12]. This seems a significant increase, as the prevalence of T2D between ages 25 and 64 was only 2.9% in 2010 [12]. However, integrated care for T2D and HT in the Cambodian PHC system remains limited [13]. More than two-thirds of the population have never had their blood glucose measured, and more than half of the population with T2D is not receiving treatment [12,14]. The proportion of patients with T2D accessing treatment is low, with few achieving recommended treatment targets [15].

The response to these T2D and HT epidemics requires concerted effort from both global health governance and Cambodia's health system. Cambodia has a pluralistic health system, with a public health care system operated by the Ministry of Health, complemented by many private health care services that mainly offer outpatient curative care, operating largely without sufficient steering and coordination from the government [16]. The government's public health care system was established based on a district health system model, following the PHC approach. With regard to the care for T2D and HT in the public health care system, the following 3 care models are being scaled up: (1) a *hospital-based model*, (2) a *health center–based model*, and (3) a *community-based model*.

The hospital-based model is a standard care model for T2D and HT that is available at district or provincial referral hospitals as part of outpatient consultation. These referral hospitals provide ambulatory care and support the health centers in treating serious cases. Health centers are allowed to take care of mild or stable cases without complications. The referral hospitals will treat serious cases [13]. In 2018, the Ministry of Health added a second component to this standard care: 29 district and provincial referral hospitals (out of 117) provided exclusive health care services for patients with T2D or HT or both in a separate section, giving explicit attention to these conditions [17].

The health center–based model has been given increasing attention by the Ministry of Health with support from the World Health Organization through the adoption of the WHO PEN for PHC [10]. The National Standard Operating Procedure for T2D and HT Management in Primary Care was developed out of the WHO PEN and approved in 2019 to strengthen implementation of the integrated basic care for T2D and HT in the PHC system. In this health center–based model, health center staff are trained to do screening, provide follow-up care for patients with T2D or HT or both with mild and stable conditions (with diagnosis only undertaken at the referral hospital), and offer health education and counseling on healthy behavior as part of screening for CVD risk factors [13]. With mild HT cases, health center staff are allowed to initiate treatment. At the health center level, care for both T2D and HT is described in a national clinical guideline on the minimum package of activities specified for health centers [18]. Yet, in practice, implementation of this guideline is not as complete as intended because the public health care system has not yet been substantially reoriented from primarily addressing acute health needs toward continuing care for chronic conditions. The public health system currently focuses on communicable diseases (HIV and AIDS, tuberculosis, malaria, diarrhea, and respiratory diseases) and maternal and child health [19]. In early 2020, only 86 health centers (out of 1221) implemented the WHO PEN program since its pilot in 2015 [17].

The community-based model is predominantly run by a Cambodian nongovernmental organization called MoPoTsyo that operates Peer Educator Networks with 4 main key services for patients with T2D or HT or both. These services include (1) self-management training through peer educator visits, (2) laboratory tests, (3) physician consultations, and (4) low-cost medicines delivered through a revolving drug fund program to the members in the network in 8 out of 24 provinces across the country. By 2019, 255 peer educators have been trained to serve over 40,000 patients [20]. In this community-based model, peer

educators, who are patients with T2D or HT or both themselves, have been trained by MoPoTsyo to be educators and counselors on lifestyle change. Peer educators also assist registered patients in the networks to have access to professional medical consultations at the public referral hospitals with which they have partnership agreements [20].

These 3 care models are implemented in isolation with relatively little interaction between each other. There have been few empirical studies on their performance. The question arises as to what extent the 3 care models have performed in providing care to people with T2D or HT or both in Cambodia. Care models that are integrated in terms of shared information and resource coordination have shown to be effective and efficient in many contexts [21]; however, implementation and scale-up of effective care models for T2D and HT remain limited, especially in LMICs. How well different models perform in contributing to good health outcomes is also not well documented. The outcomes of chronic care are difficult to measure, as such care does not have a clear end point, but requires comprehensive illness management along a continuum of care, from detection and diagnosis for initiating treatment and follow-up to successful management of the illness. This complexity requires a comprehensive framework of measurement to assess the performance of care for T2D and HT.

Inspired by noticeable successes in providing the continuum of care to people living with HIV in Cambodia [22], we adapted the HIV test-treat-retain cascade of care [23] in this study protocol to assess the continuum of care for patients living with T2D or HT or both. This method documents how many patients are lost to follow-up between the stages of testing and diagnosis, linkage with and retention in care, and adherence to treatment and control of health conditions. The cascade-of-care approach outlines the aforementioned sequential steps in long-term care. Recently, this approach has been applied to T2D and HT by pooling secondary data from cross-sectional studies of nationally representative surveys in LMICs [24,25]. This was used to produce cascades of care as an approach to assess the performance of health systems to meet the continuum of care for patients living with T2D or HT or both. Two studies, one in the United States and the other in South Africa, developed and field tested the cascade of care for T2D and HT [26,27]. Their analysis was mainly based on extracted secondary data from broader nationally representative surveys, not specifically designed for this purpose.

Given that Cambodia implements T2D and HT services through 3 different care models, we propose the cascade-of-care approach to assess the performance of these care models along the continuum of care. We will do so using primary data collection. This study protocol aims to serve as a tool to generate the cascades of care for T2D and HT for the 3 care models using the primary data of a population-based survey. The specific aims are as follows:

- To generate the cascades of care for T2D for (1) hospital-based care, (2) health center–based care (WHO PEN), (3) community-based care (Peer Educator Network), and (4) coexistence of 1, 2, and 3;
- To generate the cascades of care for HT for (1) hospital-based care, (2) health center–based care (WHO PEN), (3) community-based care (Peer Educator Network), and (4) coexistence of 1, 2, and 3;
- To compare the cascades of care for T2D between the care models 1-4;
- To compare the cascades of care for HT between the care models 1-4.

Methods

Study Design

This study protocol is part of a larger population-based survey—the SCUBY (Scale up diabetes and hypertension care for vulnerable people in Cambodia, Slovenia and Belgium) project [28], which includes other substudies focusing on (1) the health status of people aged 40 and over and the existence of comorbidities, (2) health care utilization and health care expenditure among people aged 40 and above and people living with T2D or HT or both, (3) the lifestyle and knowledge of T2D and HT among people living with T2D or HT or both, and (4) the self-management and social support for people living with T2D or HT or both.

To meet the aforesaid specific aims, 5 operational districts (ODs) in different provinces will be purposefully selected out of 103 ODs across the country. The selection is based on a mapping exercise conducted in the SCUBY project. Only in the OD Daunkeo the 3 care models coexist. The OD Samrong in a bordering province hosts a typical noncommunicable disease (NCD) clinic at the referral hospital (the WHO PEN and Peer Educator Network are not there yet). The OD Kong Pisey does not have the WHO PEN and the NCD clinic at the referral hospital (only the Peer Educator Network of MoPoTsyo exists—with relatively strong network). The OD Pearaing is one of the ODs piloting the WHO PEN and started implementing the program since 2015. At the time of study, 8 of 9 health centers have implemented the WHO PEN. The OD Sotr Nikum is historically and significantly influenced by the financial aid of various development partners and nongovernmental organizations—contextual factor is a focus. The referral hospital in this OD has a Chronic Disease Clinic, where people with T2D or HT or both and those with HIV seek treatment and care [29]. At the time of study, 5 of 25 health centers have implemented the WHO PEN. Table 1 shows the existence of care provision for T2D and HT in each OD.

Table 1. Selected provinces and ODs[a] with different types of care models.

OD name	Province	Existing care provision	Care model
Samrong	Oddar Meanchey	NCD[b] clinic at the referral hospital	Hospital-based care
Pearaing	Prey Veng	NCD clinic[c] + WHO PEN[d] (high coverage)	Health center–based care
Sotr Nikum	Siem Reap	NCD clinic[c] + WHO PEN (low coverage)	Health center–based care with context
Kong Pisey	Kampong Speu	Peer Educator Network[e]	Community-based care
Daunkeo	Takeo	NCD clinic + WHO PEN + Peer Educator Network	Coexistence of care

[a]OD: operational district.

[b]NCD: noncommunicable disease.

[c]In the WHO PEN implementation arrangement, the referral hospital in the OD supports the health centers in providing the secondary care.

[d]WHO PEN: World Health Organization Package of Essential Noncommunicable Disease Interventions.

[e]The Peer Educator Network arranges a medical consultation for their registered patients once a week at the referral hospital in the OD.

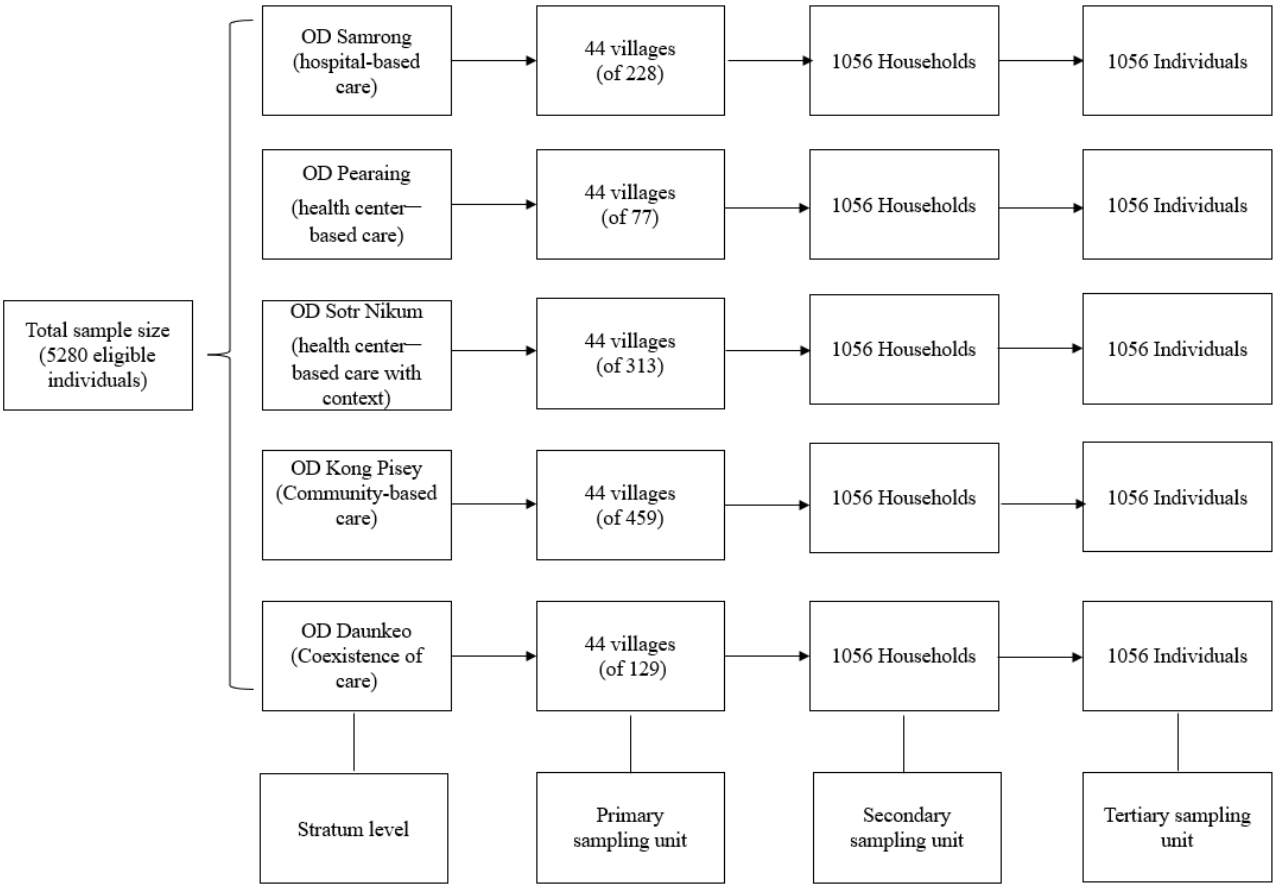
This population-based survey includes 2 questionnaires (Multimedia Appendices 1 and 2). One questionnaire is directed at household heads and inquires about the household's socioeconomic status, member characteristics, general health of the household members, and their access to health care and health-related expenditure. The other questionnaire is for eligible adults (ie, adults aged ≥40) of the selected households and inquires about their sociodemographic information, health status and comorbidity, quality of life, health care utilization, social support, behavioral measurements, and knowledge of T2D and HT for known patients with T2D or HT or both in particular. Known patients with T2D or HT or both are also asked about their medical adherence and decision-making power over diet.

Sampling and Sample Size

This population-based survey follows a multistage stratified random cluster sampling [30]. For the sampling procedure, each OD is considered as a stratum due to the care model present (Table 1). Based on rules of stratification, each stratum is theoretically independent from one another, and its selection can be based on the aforementioned specific aims [30]. In each stratum, clusters of primary sampling units (villages) will be randomly sampled.

Based on the multistage stratified random cluster sampling, 3 stages of stratification are applied, and in each stage randomization is employed. ODs are the strata, and health centers impacted by the types of care models are selected. For the first stage of stratification, sampling with equal probability (equal probability selection method) will be used to determine the number of villages under the catchment areas of the impacted health centers in each OD. This equal selection is also made to ensure oversampling for some ODs. If using proportionate allocation of the sample units across the ODs, the sample selected from the ODs representing certain types of care models would be too low to have enough statistical power for the analyses. In this survey, disproportionate allocation is done to randomly select equal-sized samples in the 5 ODs [30]. For the second stage of stratification, households having adult(s) aged 40 and above (secondary sampling units) in the selected villages are selected and listed. Systematic random sampling is used to select the households from each village. For the third stage of stratification, only 1 individual meeting the eligibility criteria (described later) is randomly selected from each household to reduce the clustering effect. Thus, 1 eligible individual is selected from each household, making the total sample size of eligible individuals the same as the sample size of households (Figure 1).

Figure 1. Flow of the sampling frame.



The sample size of households in all the selected 5 ODs is calculated based on the following formula [30]:

$$n_h = (z^2)(r)(1–r)(f)(k)/(p)(\gamma)(e^2)$$

where n_h is the parameter to be calculated and the sample size in terms of the number of households to be selected; z is the statistic that defines the level of confidence desired (1.96 for the 95% level of confidence); r is an estimate of a key indicator to be measured by the survey (the key indicator being T2D prevalence—this r being 0.1 according to 10% of T2D prevalence among adults aged 40 and over—the national STEPS survey 2016 [12]); f is the sample design effect (1.5 used in accordance with the national STEPS survey 2016 [12] and the Cambodian demography and health survey 2014 [19]); k is a multiplier to account for the anticipated rate of nonresponse (1.2 for 20% anticipated rate, as used in the national STEPS survey 2016 [12]); p is the proportion of the total population accounted for by the target population and upon which the parameter r is based (0.24 for 24% [31]); γ is the average household size (4.6 for the number of persons per household in the selected provinces—census 2019 [32]); and e is the margin of error to be attained (0.01 for the level of precision at 10% of r).

While HT prevalence is higher, T2D prevalence of 10% [12] is used as the main key indicator of interest to determine the sample size, which is important for the cascade of care. Based on the aforementioned formula, the total sample size would be 5637 households, including 20% of anticipated nonresponse rate. Enlarging the sample size to include enough patients to assure significant differences for the detection of the number of patients with T2D having blood glucose under control would increase the budget 5-fold, which is not feasible. Taking feasibility and budget constraint into consideration, a fixed cluster size of 24 households per village, with 44 villages randomly selected in each OD, will be applied for the sake of controlling the total sample size and interviewer workloads [30]. Thus, a cluster size of 24 households per village over the total villages of 220 would yield the total sample size of 5280 households (also equal 5280 eligible individuals).

Target Population and Recruitment Strategy

Adults aged 40 and above are the target population. This age group is appropriate for screening for T2D and HT according to the national standard operating procedure for T2D and HT management in primary care [13]. Other recruitment criteria include (1) being usual members of the household, having stayed in the household the night before the interview or not been absent for more than 6 months; (2) being physically and mentally capable of answering the questions; and (3) providing consent to participate in the study.

The starting point of recruitment is a list of all the eligible households in the selected villages (Multimedia Appendix 3). The list will be constructed by a listing team with support of a local authority, listing households in the selected village having at least one adult aged 40 and above. When a household is selected, 1 household member aged 40 and above will be selected for inclusion in the study. If the selected eligible individual is not present in the household during the first-time

visit, 2 repeated callbacks and follow-up will be applied. Only if all these attempts fail, the selected participants would be replaced: the respective households would be replaced with the next household in a row of the eligible household list constructed. The replacement household would be selected following the procedure described earlier. If the eligible individuals can be contacted but express refusal to participate in the study after a few times of failed explanation, the individuals as well as the households would be dropped from the study.

Data Collection Procedure

Data collection process will follow the STEPS survey approach [33], with modification of the sequence of the steps to adapt the data collection to the study context. There are 3 main steps of data collection: (1) structured interviews with questionnaires, (2) anthropometric measurements, and (3) biochemical measurements. The modification will entail data collectors taking anthropometric measurements and biochemical measurements of the eligible individuals before administering the 2 sets of questionnaires.

The anthropometric measurements include measurements of blood pressure, body weight, height, and waist and hip circumferences. For blood pressure measurements, participants will rest at least 15 minutes prior to the measurement and 3 readings will be taken 3 minutes apart from one another, with the left arm recommended for the measurement [33]. For the biochemical measurements, testing of fasting blood glucose (FBG) will be carried out for all the participants (Multimedia Appendix 4) and glycated hemoglobin A_{1c} (HbA_{1c}) and creatinine for known participants with T2D or participants having FBG of 126 mg/dl or more (Multimedia Appendix 5). Data will be digitally collected using the KoBoToolbox system developed by the Harvard Humanitarian Initiative [34].

For the point-of-care measurement of FBG (capillary plasma value), the On Call Plus (ACON USA), which is compliant with the US Food and Drug Administration regulations [35], will be used. It is widely used in the WHO PEN program in Cambodia. The HemoCue HbA_{1c} 501 System, whose quality is ensured by the International Federation of Clinical Chemistry and Laboratory Medicine and the National Glycohemoglobin Standardization Program [36], will be employed as a point-of-care test for HbA_{1c}. Regarding the anthropometric measurement, Omron JPN500, which is clinically validated by the Association for the Advancement of Medical Instrumentation and European Society of Hypertension [37], will be used to measure blood pressure. A flat weight scale (Seca-803), height measuring system (Seca-217), and ergonomic circumference measuring tape with extra waist-to-hip-ratio calculator (Seca-203) will be used to measure weight, height, and waist and hip circumferences of the participants, respectively. Seca is internationally recognized as producing highly accurate scales equipped with high-precision measuring technology [38].

Statistical Analysis Plan

For the analysis plan, 6 cascade bars, as explained in Tables 2 and 3, will be used to generate the cascades of care for T2D and HT, respectively. A fixed denominator approach will be followed as it enables readers to see the leakages between stages of the continuum of care [39]. The denominator is the total number of eligible individuals aged 40 and above having T2D (for the T2D cascade of care) and HT (for the HT cascade of care). We will produce the cascade of care for T2D and HT for the selected ODs hosting different existing care models. These cascades of care—in essence, a series of bar charts—will subsequently be translated into cumulative probabilities. The bivariate analysis will be used to identify potential factors associated with the outcome variables—prevalence, testing, diagnosis, in care, in treatment, and under control bars. At the initial stage, the chi-square test will be used to determine the association between explanatory variables and outcome variables. The explanatory variables will include participants' age, sex, marital status, educational level, household wealth quintile, health care utilization, and care model setting. Variables with statistically significant level ($P<.2$) will be included in a multiple logistic regression model. In addition to the aforementioned variables, BMI, lifestyle, knowledge of T2D and HT, self-management, and social support will be included in the multiple logistic regression model for the outcome variables—in care, in treatment, and under control bars [24,25]. In the multiple logistic regression model, the backward elimination method will be used. The process will start with all the identified explanatory variables. Then, variables with the highest *P* value will be eliminated from the model one by one at a time. The process will be repeated until all the variables in the model are statistically significant with a cut-off point of *P* value <.05. This knowledge will allow us to identify which characteristics stimulate the probability of not reaching the next step in the cascade of care, thereby identifying patient groups not adequately reached.

Table 2. Defined groups of participants for each bar of the cascade of care for T2D[a].

Bars of the cascade of care for T2D	Definitions	Questions extracted for analysis
1. Prevalence of the target population living with T2D	• Participants having biochemical measurement of FBG[b] (capillary plasma value) ≥126 mg/dl (7 mmol/L) and HbA_{1c}[c] level ≥6.5% [24,40,41] • or Participants reporting use of drugs for T2D, irrespective of their biomarker values	• Measurement of FBG • Measurement of HbA_{1c} • Have you ever been told by a doctor or other health worker that you have T2D?
2. Number of the target population with T2D ever tested for T2D	• Classified patients with T2D having had FBG tested in the last 3 years	• Have you ever had your blood glucose tested in the last 3 years?
3. Number of those tested ever diagnosed for T2D	• Tested patients with T2D reporting ever being told by a doctor or other health worker as having T2D	• Have you ever been told by a doctor or other health worker that you have T2D?
4. Number of those diagnosed in care	• Diagnosed patients with T2D reporting getting treatment/care for their conditions at least once in the past 12 months	• Did you get treatment/care for your T2D condition in the past 12 months?
5. Number of those in care receiving treatment	• In-care patients with T2D reporting using drugs for T2D or insulin in the past 2 weeks or in-care patients with T2D reporting following advice to lose weight, stop smoking, do physical exercise, and be on special prescribed diet	• Are you currently receiving any of the following treatment/advice for your T2D condition prescribed by a doctor or health care worker? • Insulin or drugs (medication) that you have taken in the past 2 weeks • Are you currently receiving any of the following treatment/advice for your T2D condition prescribed by a doctor or health care worker? • Special prescribed diet and • advice to lose weight and • advice to stop smoking and • advice to start or do more physical exercise
6. Number of those receiving treatment being under control	• In-treatment patients with T2D having HbA_{1c} level <8% [24]	• Measurement of HbA_{1c} for the known T2D

[a]T2D: type 2 diabetes.

[b]FBG: fasting blood glucose.

[c]HbA_{1c}: glycated hemoglobin A_{1c}.

Table 3. Defined groups of participants for each bar of the cascade of care for HT[a].

Bars of the cascade of care for HT	Definitions	Questions extracted for analysis
1. Prevalence of the target population living with HT	• Participants having systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg [12] or	• Measurement of blood pressure (mean of the second and third readings)
	• Participants reporting use of drugs for HT, irrespective of their blood pressure values	• Have you ever been told by a doctor or other health worker that you have HT?
2. Number of the target population with HT ever tested for HT	• Classified patients with HT having had a blood pressure measured in the last 3 years	• Have you ever had your blood pressure measured in the last 3 years?
3. Number of those tested ever diagnosed for HT	• Tested patients with HT reporting ever being told by a doctor or other health worker as having HT	• Have you ever been told by a doctor or other health worker that you have HT?
4. Number of those diagnosed in care	• Diagnosed patients with HT reporting getting treatment/care for their conditions at least once in the past 12 months	• Did you get treatment/care for your HT condition in the past 12 months?
5. Number of those in care receiving treatment	• In-care patients with HT reporting using drugs for HT in the past 2 weeks or	• Are you currently receiving any of the following treatment/advice for your HT condition prescribed by a doctor or other health worker? • Drugs (medication) that you have taken in the past 2 weeks
	• In-care patients with HT reporting following advice to lose weight, stop smoking, do physical exercise, and reduce salt intake	• Are you currently receiving any of the following treatment/advice for your HT condition prescribed by a doctor or other health worker? • Advice to reduce salt intake and advice to lose weight and advice to stop smoking and advice to start or do more physical exercise
6. Number of those receiving treatment being under control	• In-treatment patients with HT having systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg [12]	• Measurement of blood pressure (mean of the second and third readings) for the known HT

[a]HT: hypertension.

Because of the multistage stratified random cluster sampling, a 3-stage weighting procedure will be applied to account for (1) the fixed number of villages selected in each OD, (2) the fixed number of households selected in each village, and (3) the number of household members aged 40 and above in each selected household [25,30]. The statistic program Stata 14.2 (StataCorp) [42] will be used to perform the quantitative analyses.

Variables used to generate the cascade of care for T2D and HT are shown in Tables 2 and 3, respectively. The explanatory variables are detailed in Multimedia Appendix 6 [43-47].

The population in the catchment areas is not confined to seek care only in the designated public health facility. To address this, we will also collect patient registry data from the public health facilities in the study setting with regard to patients receiving treatment for triangulating the care model selected.

Ethics Approval

This study protocol has been approved by the National Ethics Committee for Health Research in Cambodia (reference number 105 NECHR) and by the Institutional Review Board of Institute of Tropical Medicine (Antwerp; reference number 1323/19). The study is also registered as part of the SCUBY protocol at the International Standard Randomised Controlled Trials Number (ISRCTN) registry, number ISRCTN41932064 (first date of publication February 3, 2020).

Results

Data collection was carried out from mid-July to mid-October 2020. By June 2021, the data cleansing process was finished and cleaned data were properly managed as data sets. As of December 2021, the recruitment process was completed, with 5072 eligible individuals participating in the data collection; however, data analysis is pending. Results are expected to be fully available in mid-2022.

Discussion

This protocol aims to assess the performance of the 3 dominant care models for T2D and HT through the cascade of care framework, using the population-based survey. This framework will allow us to identify the leakages in the system and the unmet need for care [24]. In addition, we will be able to better

understand the diversity in service models across the country by comparing 3 different care models. The design of this study, using large-scale primary data, is unique. The evidence generated from this large-scale survey of more than 5000 households will stimulate policy-relevant analysis that is informative to the existing care for T2D and HT provided by the 3 main care models and act as baseline data for progress monitoring purposes [24]. Identifying gaps in the health system is vital to improve efficiency and effectiveness of its performance.

The strengths of the study are primary data collection, a large sample size, and multiple types of data. This allows us to assess multiple outcomes and to link them with other indicators such as health care utilization, health seeking behavior, morbidity profile, and sociodemographic characteristics. The limitations relate to its complicated set up. The multilevel stratification and the collection of multiple types of (outcome) data make the research design and practical organization difficult. The clustering on more than 2 levels and the different outcomes make it challenging to calculate an ideal sample size following all regulations. We have addressed this by seeking optimal balance between maximizing precision and minimizing costs for feasibility. The purposive selection of ODs based on the mapping of existing care models limits the generalizability of results. However, through randomization within ODs, we will strive for maximum internal validity.

Despite these limitations, this study protocol has a large potential to produce evidence of the performance of different care models for T2D and HT in Cambodia. These insights will help implementers and policy makers to assess scale up and adapt strategies. This is of vital importance owing to the increasing burden of CVDs, T2D, and HT in the country [5,12,13]. As many LMICs struggle with similar burdens of disease and similar structural problems in their health systems, the study protocol and its expected results are also useful for monitoring and scaling up of care for highly prevalent chronic diseases across the globe.

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors took part in conceptualizing the study design. VT prepared the original draft. EW, JvO, VB, WVD, and PI provided feedback on the drafts. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire about household information.
[PDF File (Adobe PDF File), 485 KB - resprot_v11i9e36747_app1.pdf]

Multimedia Appendix 2
Questionnaire about eligible individual information.
[PDF File (Adobe PDF File), 1028 KB - resprot_v11i9e36747_app2.pdf]

Multimedia Appendix 3
Sample list of the eligible households in each village.
[PDF File (Adobe PDF File), 128 KB - resprot_v11i9e36747_app3.pdf]

Multimedia Appendix 4
Sample record book of anthropometric and biochemical measurements of all the eligible individuals.
[PDF File (Adobe PDF File), 137 KB - resprot_v11i9e36747_app4.pdf]

Multimedia Appendix 5

Sample record book of HbA_{1c} and Creatinine measurements of known T2D patients or the eligible individual having FBG ≥126 mg/dl.
[PDF File (Adobe PDF File), 163 KB - resprot_v11i9e36747_app5.pdf]

Multimedia Appendix 6
Identified explanatory variables.
[PDF File (Adobe PDF File), 255 KB - resprot_v11i9e36747_app6.pdf]

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Abbreviations

CVD: cardiovascular disease
FBG: fasting blood glucose
HbA_{1c}: glycated hemoglobin A_{1c}
HT: hypertension
LMIC: low- and middle-income country
NCD: noncommunicable disease
OD: operational district
PHC: primary health care
SCUBY: Scale up diabetes and hypertension care for vulnerable people in Cambodia, Slovenia and Belgium
STEPS: STEPwise approach to NCD risk factor surveillance
T2D: type 2 diabetes
WHO PEN: World Health Organization Package of Essential Noncommunicable Disease Interventions

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Protocol

Measuring Microtemporal Processes Underlying Preschoolers' Screen Use and Behavioral Health: Protocol for the Tots and Tech Study

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Abstract

Background: Excessive screen time is associated with poor health and behavioral outcomes in children. However, research on screen time use has been hindered by methodological limitations, including retrospective reports of *usual* screen time and lack of momentary etiologic processes occurring within each day.

Objective: This study is designed to assess the feasibility and utility of a comprehensive multibehavior protocol to measure the digital media use and screen time context among a racially and economically diverse sample of preschoolers and their families. This paper describes the recruitment, data collection, and analytical protocols for the Tots and Tech study.

Methods: The Tots and Tech study is a longitudinal, observational study of 100 dyads: caregivers and their preschool-age children (aged 3-5 years). Both caregivers and children will wear an Axivity AX3 accelerometer (Axivity Ltd) for 30 days to assess their physical activity, sedentary behavior, and sleep. Caregivers will complete ecological momentary assessments (EMAs) for 1 week to measure child behavioral problems, caregiver stress, and child screen time.

Results: The Tots and Tech study was funded in March 2020. This study maintains rolling recruitment, with each dyad on their own assessment schedule, depending on the time of enrollment. Enrollment was scheduled to take place between September 2020 and May 2022. We aim to enroll 100 caregiver-child dyads. The Tots and Tech outcome paper is expected to be published in 2022.

Conclusions: The Tots and Tech study attempts to overcome previous methodological limitations by using objective measures of screen time, physical activity, sedentary behavior, and sleep behaviors with contextual factors measured by EMA. The results will be used to evaluate the feasibility and utility of a comprehensive multibehavior protocol using objective measures of mobile screen time and accelerometry in conjunction with EMA among caregiver-child dyads. Future observational and intervention studies will be able to use this study protocol to better measure screen time and its context.

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KEYWORDS

ecological momentary assessment; accelerometery; objective screen time monitoring; mobile phone

Introduction

Background

Excessive screen time for children is linked with poor sleep, inactivity, and behavioral problems [1-4], and only few children meet the World Health Organization's recommendation that children under 5 years receive ≤1 hour of screen time per day [5,6]. The ways in which families use screens have changed dramatically over the past 2 decades, in large part owing to the introduction of mobile and interactive digital media devices. Historically, children's screen time comprised mostly television use, which took place mainly at home. With new forms of digital media such as mobile phones and tablets, families can now use screens across many different locations and contexts. The pervasive availability of mobile devices has resulted in a dramatic increase in children's use of mobile media. Children's mobile screen time increased from 5 minutes per day in 2011 to 55 minutes per day in 2020, with nearly half (46%) of the children aged 2 to 4 years and more than two-thirds (67%) of the children aged 5 to 8 years having their own mobile device (tablet or smartphone) [7]. Videos on the web now constitute two-thirds of children's screen viewing (66%), supplanting traditional television, which now accounts for only 23% of the average daily video screen time [7]. Unfortunately, our understanding of mobile screen use and its impact on child health lags behind the accelerated adoption of mobile technology.

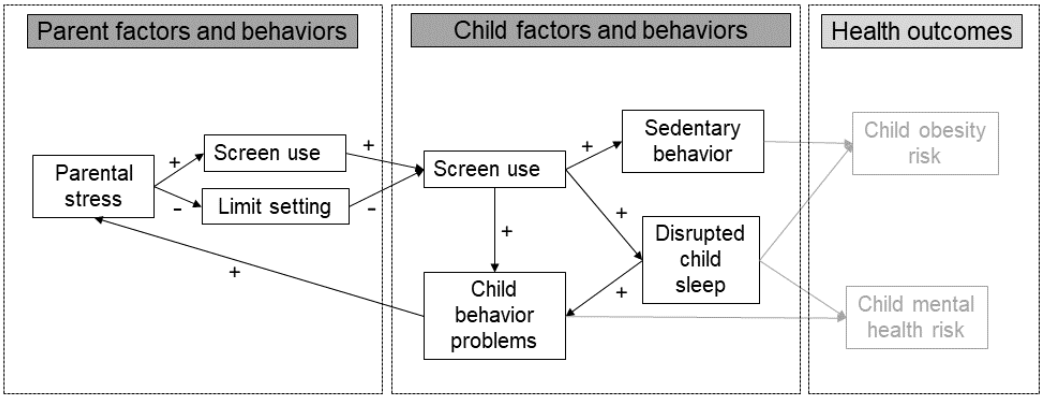
Measuring screen time is complicated and has historically relied upon time-consuming, expensive observational methods conducted by highly trained staff or upon parent recall survey methods [8-12]. In a 2021 systematic review of young (aged 0-6 years) children's screen time, none of the 622 studies used an objective measure of screen time [13]. However, there was only a moderate correlation between self-reported and objectively observed media use (r=0.38). Of the 49 studies that examined adults' digital media–use behaviors, only 3 were within 5% of their objectively measured mean [10]. Another important limitation of commonly used screen time measures is their provision of global estimates of screen use, which is often gathered from a single question that asks parents to estimate television use in a *typical* day [14,15]. This global measure of screen time precludes the ability to examine the context or timing of screen use within and across days, thus limiting the understanding of the complex and changing patterns of children's daily screen use. Therefore, updated, objective, and low-burden measures of screen use and its context are needed.

Recent developments in the passive monitoring of mobile screen use have the potential to provide novel insights into how, when, where, and why children and families use digital media (ie, mobile phones and tablets) throughout the day [16-18]. This method of digital media monitoring is both less expensive than direct observation and less burdensome for participants than self-reporting measures [15]. Similarly, advances in ecological momentary assessments (EMAs) allow for the assessment of the context and timing of behaviors while minimizing recall bias. Finally, advances in accelerometry have made it possible to passively collect continuous 24-hour data on children's sedentary behavior, physical activity, and sleep over extended periods (ie, 30 days). While these technologies have been tested in isolation [8,16,19,20], to date, no studies have leveraged multiple streams of data from passive mobile sensing, EMA, and accelerometry to specifically study young children's screen time [13,21]. It is unclear whether the confluence of these methods can be successfully used to gather meaningful information about the digital media use of children and families. Furthermore, the emerging literature on passive mobile sensing has been conducted with high-income White families and may not be generalizable [8,16].

Objective

We aim to evaluate the feasibility and utility of a comprehensive multibehavior protocol to measure digital media use and screen time context among a racially and economically diverse sample of preschoolers and their families. Figure 1 depicts the conceptual model of the associations between screen time context and children's behaviors.

Figure 1. Conceptual model of proximal and distal associations among screen use, parent behaviors, and child behaviors.



Methods

Design Overview

This study includes 100 caregiver-child dyads and uses a longitudinal, observational, dyadic, case-crossover design [22]. Using a case-crossover design allows a dyad to serve as its own control to assess the within-day effects of immediate antecedents on a dependent variable measured multiple times throughout the day and week [22]. Caregivers and their children aged 3 to 5 years will participate in a 30-day assessment protocol, with 50% (50/100) of the sample invited to participate in a second wave of data collection 3 to 12 months later to evaluate the feasibility of retaining the sample over time and to assess the longer-term acceptability of the protocol.

Participants

Participants include racially and economically diverse caregivers and preschoolers in the greater Southeastern United States. The caregiver inclusion criteria are as follows: (1) being a primary caregiver of a child between the ages of 3 and 5 years, (2) owning a smartphone device, and (3) being able to read and speak English. The exclusion criteria for children include a diagnosis of a severe developmental or physical disorder that would prevent ambulation. This decision was made because of the inability to recruit a large enough sample of children to draw meaningful conclusions.

Procedures

The study maintains rolling recruitment, with each dyad on their own assessment schedule, depending on the time of enrollment. Enrollment was scheduled to take place between September 2020 and May 2022.

We aim to recruit a nonrandom volunteer sample by posting fliers at daycare centers, pediatric clinics, and community centers such as food banks, as well as Facebook advertising in the form of "boosted" posts. To obtain a socioeconomically diverse sample, we will partner with daycares serving low-income families and prioritize the enrollment of low-income families. In addition, we will use snowball recruitment methods where participants are compensated for referring families who then successfully participate in the study.

Data collection is completely remote, in part driven by the necessary COVID-19 pandemic protocol adjustments [23]. Interested participants will be directed to an informational website through a QR code or hyperlink. The informational website describes the study procedures and research participant protections. The informational website includes a web-based consent form and directs interested participants to a short screener survey to assess initial study eligibility. A trained member of the research team will contact interested and eligible families by phone to answer any remaining questions and verbally confirm their desire to participate.

Following recruitment, the eligible child and caregiver dyads are texted a Qualtrics link to the baseline survey. The baseline questionnaire is designed to be completed within approximately 30 minutes. After caregivers complete the baseline survey, they are sent instructions to download a screen time monitoring app (Chronicle; Android devices) [18] or upload screenshots (iOS devices) depending on the make of their smartphone. Technical support is provided as required by the research team. Caregivers are then mailed 2 Axivity AX3 accelerometers (Axivity Ltd), one for themselves and one for their preschool-age child. Caregivers and their children are asked to wear the Axivity AX3 and monitor their screen time for 30 days. We will conduct a 30-day assessment to examine the higher limit of time that the families are willing to wear an activity watch and monitor their digital media use. The first week of the 30-day monitoring period includes 7 days of EMAs, which are texted to the primary caregivers' smartphones. EMAs are limited to the first week (vs the entire monitoring period) to minimize participant burden, as this portion of the study requires active participation. The first week of the 30-day assessment was selected to allow for flexibility because of any potential issues that might prevent a participant from completing EMAs (eg, work conflicts). Participants who do not complete enough EMAs to earn a gift card during the first week (Compensation section) are offered an extension to complete additional EMAs. In line with the recent EMA studies [20], the Tots and Tech study allows flexibility in the survey completion window in an effort to retain families from diverse backgrounds who might experience additional barriers to completing measures within the time frame. Following the 30-day monitoring protocol, caregivers will complete a semistructured qualitative interview about their experiences. Participants who complete the study protocol (eg, do not drop out) in the first year (wave 1) are randomly selected (50/100, 50%) to be recontacted 3 to 12 months after the initial evaluation and invited to repeat the entire research protocol for additional compensation. Families that decline to participate in the second assessment are asked to complete a short web-based survey regarding their experiences and reasons for declining. The number of families that decline or are lost to follow-up is documented to assess protocol feasibility.

Baseline Survey

Overview

The following information is assessed using survey measures administered through the Qualtrics platform. Caregivers report on the following sociodemographic variables for themselves and their child: birthday, biological sex, and race and ethnicity. Caregivers indicate their relationship with the child, marital status, employment status, and education, as well as the following household characteristics: number of children and adults in the home, family income, and use of government assistance (eg, Supplemental Nutrition Assistance Program or Special Supplemental Nutrition Program for Women Infants and Children, medical assistance, etc). *Poverty ratio* is calculated based on the caregiver's report of family income and number of dependents using federal poverty thresholds that align with the year of data collection [24]. Caregivers complete the 2-item *food insecurity* screening questionnaire. This 2-item screener has shown excellent sensitivity and specificity (93% and 87%, respectively) with the 18-item US Department of Agriculture household food security scale [25], which is considered the gold standard for assessing food insecurity among children [26]. A 1-item measure is used to assess neighborhood safety, "How safe do you consider your neighborhood?" [27] Caregivers

complete retrospective measures of chronic stress, including *perceived stress* in the past month (Perceived Stress Scale) [28] and confusion and *disorganization* in the home environment (CHAOS) [29], in addition to measures of *symptoms of depression and anxiety* (Center for Epidemiological Studies-Depression Scale and State-Trait Anxiety Inventory, respectively) [30,31]. Caregivers also complete measures assessing *child behaviors* (Strengths and Difficulties Questionnaire) [32] *and parenting satisfaction* [33]. Caregivers complete questionnaires regarding their child's and their own *sleep habits* and routines [34-36] and *screen time* habits [37], function [38], and regulations [39], in addition to the number and types of screens in the home and in the child's bedroom.

Height and Weight

Owing to COVID-19 pandemic restrictions [23], caregiver and child height and weight are collected via caregiver report on the baseline survey. BMI (kg/m^2) is calculated for caregivers. As for children, age- and sex-specific BMI z-scores are determined using the Centers for Disease Control and Prevention criteria [40].

EMA Surveys

Caregivers will complete the EMA surveys in the first week of the 30-day protocol. EMA surveys are sent to caregivers via SMS text messages to their smartphones. The SMS text messages contain a Qualtrics survey link to assess the domains using prompts listed in Table 1. Additional items that are only included in the end-of-day survey are listed in Table 2.

Table 1. Ecological momentary assessment (EMA) items.

Variable domain and item	Response options	Frequency or format
Time spent with child		
• How much time have you spent with your child in the past 2 h?	• None • <30 min • 30-60 min • 60-90 min • 90-120 min	If "none," skip to Stress Exposure questions
Child mobile phone use		
• In the last 2 h, how much has your child used your mobile phone?	• None • <30 min • 30-60 min • 60-90 min • 90-120 min	Select one
Child other screen time		
• In the last 2 h, how much has your child watched television, played videogames, or used a computer?	• None • <30 min • 30-60 min • 60-90 min • 90-120 min	If "none" on both Child Mobile Phone Use and Child Other Screen Time, skip Screen Function question
Screen function [38]		
• I let my child use these screens...	• So that they could learn something • As a reward for good behavior • As they like it • As part of a daily routine • To allow myself free time	Select all that apply
Child behavior problem intensity [41]		
• In the last 2 h, how problematic has your child's behavior been?	• Not at all • A little bit • Moderate amount • Quite a bit • A great deal	Select one
Child behavior problem content [42]		
• Did your child lose their temper/have a temper tantrum in the last 2 h?	• Yes • No	Select one
• Did the tantrum last >5 min?	• Yes • No	If "yes" to the previous question
• Was this tantrum because they were...	• Frustrated, angry, or upset • Tired hungry or sick • To get something she/he wanted • Out of the blue	If "yes" to the previous question; select all that apply
• Did your child disobey or break the rules/say "no" when told to do something in the last 2 h?	• Yes • No	Select one
• Did your child disobey or break the rules/say "no" because they were...	• Frustrated, angry, or upset • Tired hungry or sick • To get something she/he wanted • Out of the blue	If "yes" to the previous question; select all that apply
• Did your child act aggressively in the last 2 h?	• Yes • No	Select one

Variable domain and item	Response options	Frequency or format
• Did your child act aggressively because they were...	• Frustrated, angry, or upset • Tired hungry or sick • To get something she/he wanted • Out of the blue	If "yes" to the previous question; select all that apply
Stress exposure [43]		
• In the last 2 h, which of these things caused you stress?	• Work • Demands at home • Family • Tension with a coworker • Tension with a partner • Tension with your child • Something else	Select all that apply
Stress [44]		
• How stressed are you feeling right now?	• Not at all • A little • Quite a bit • Extremely	Select one
Perceived stress or self-efficacy [45]		
• How certain do you feel that you can deal with all the things that you have to do RIGHT NOW?	• Not at all • A little • Quite a bit • Extremely	Select one
Affect [46]		
• How frustrated/angry are you feeling? • How sad/depressed are you feeling? • How happy are you feeling? • How calm/relaxed are you feeling?	• Not at all • A little bit • Moderate amount • Quite a bit • Extremely	Select one
Physical context		
• Where were you when you received this message?	• Home (indoors) • Home (outdoors) • Work (indoors) • Outdoors (not at home) • Indoors (not at home) • Car/bus/train • Other (specify)	Select one

Table 2. Ecological momentary assessment (EMA) prompts for end of day.

Variable domain and item	Response options	Frequency or format
Parent sleep quality [35]		
How would you rate YOUR sleep quality last night?	• 0 (terrible) to 5 (excellent)	Select one
Child sleep quality [47]		
How would you rate your CHILD'S sleep quality last night?	• 0 (terrible) to 5 (excellent)	Select one
Child behavior		
Thinking back on today, how often did your child misbehave in ways that were dangerous or unsafe?	• Not at all • Once • More than once	Select one
Thinking back on today, how often did your child act aggressively toward adults?	• Not at all • Once • More than once	Select one
Screen time limiting		
How much did you stick to your "usual" rules around screen time?	• 1 (not at all) to 5 (completely)	Select one
Bedtime rules		
How much did you stick to your "usual" routines and rules around bedtime?	• 1 (not at all) to 5 (completely)	Select one
Mobile screen time		
For how many hours did your child use your mobile phone today?	• 0-12+ h	Select one
Interactive screen time		
How many hours did your child use a tablet or computer or play video games today?	• 0-12+ h	Select one
Passive screen time		
How many hours did your child watch television, videos, movies (not on a mobile device) today?	• 0-12+ h	Select one
Time spent with the child [41]		
Since waking up this morning, how many hours have you spent with your child in the same location?	• 0-12+ h	Select one
Daycare		
How many hours did your child attend preschool/daycare today?	• 0-10+ h	Select one
Parent illness		
Were you sick today?	• Yes • No	Select one
Child illness		
Was your child sick today?	• Yes • No	Select one
Accelerometer compliance-parent		
Did you wear the activity watch all day today?	• Yes • No	Select one
If not, why?	• Lost/cannot locate • Strap broken • Uncomfortable • Other (specify)	If "no" to the previous question

Variable domain and item	Response options	Frequency or format
Accelerometer compliance-child		
Did your child wear the activity watch today?	• Yes • No	Select one
If not, why?	• Lost/cannot locate • Strap broken • Uncomfortable • Other (specify)	If “no” to the previous question

Caregivers are informed that they will receive 4 “short surveys” per day between 8:30 AM and 9 PM and that they have 2 hours to complete each survey. For example, if a survey is sent at 8:30 AM, caregivers will have until 10:30 AM to complete the survey. After 2 hours, the links expire, and caregivers will no longer be able to access the survey. The schedule of assessments differs over the course of the 7 days and thus appears random to participants. The exact schedule is presented in Table 3. The timing protocol uses 4 signal-contingent prompts, including 1 end-of-day EMA message, which occurs at 9 PM every night. The EMA surveys are delivered in nonoverlapping time windows and refer to the previous 2 hours. This timing was selected based on previous research indicating that ≤5 prompts per day are acceptable to families [48].

Table 3. Ecological momentary assessment (EMA) schedule[a].

Day	Time			
Monday	9:30 AM	1 PM	7 PM	9 PM
Tuesday	8:30 AM	2 PM	7:30 PM	9 PM
Wednesday	9:30 AM	2:30 PM	6 PM	9 PM
Thursday	9 AM	2 PM	7:30 PM	9 PM
Friday	10:30 AM	3:30 PM	7 PM	9 PM
Saturday	9:30 AM	3 PM	7 PM	9 PM
Sunday	10 AM	2 PM	6 PM	9 PM

[a]Participants will receive an SMS text message at these times prompting them to complete an ecological momentary assessment that must be completed within 2 hours.

In line with the recent guidelines for EMA use [49], caregivers are provided training on completing the EMAs and given a practice opportunity before the start of the assessment period. Training comprises 1 practice EMA and 1 practice end-of-day survey (with additional questions at the day level), and participants have the opportunity to seek clarity on the survey items and procedures before the assessment period.

First, caregivers report how much time they have spent with their child over the previous 2 hours. Caregivers who indicate that they have not been with their child are not presented with survey items regarding their child’s behaviors. EMA prompts regarding the frequency and intensity of child behavioral problems are based on EMA items previously tested among parents of young children [41]. Items regarding specific disruptive behavior are adapted from the Multidimensional Assessment of Preschool Disruptive Behavior [42]. Exposure to stressors is assessed using items adapted from the Daily Hassles Scale [43,50]. Degree of stress is assessed from a single item, “How stressed are you feeling right now?” Responses range from “not at all” to “extremely” [44]. Time Spent with Child and Limit Setting items are informed by existing protocols using EMA among parents [43]. Caregiver report of the overall screen time is assessed using questions adapted from the National Health and Nutrition Examination Survey screen time survey [51]. Daily assessment of screen time is presumed to improve recall bias compared with 30-day recall measures.

Several methodological considerations were made when designing the EMA protocol to balance the benefits of data richness with the drawbacks of potential participant burden and demand characteristics. Reduced-item EMA subscales are used instead of the full scales in order to limit survey fatigue. In addition, EMA surveys are prompted at seemingly random times within preset intervals (ie, a hybrid signal-interval contingent sampling schedule) to prevent anticipatory effects, such as pausing or changing current behavior in anticipation of a survey prompt at a known time [52]. Despite the use of repeated measures, reactivity is generally low with EMA procedures [53]. Furthermore, the combination of EMA with accelerometer data minimizes the weakness of using either instrument independently [54].

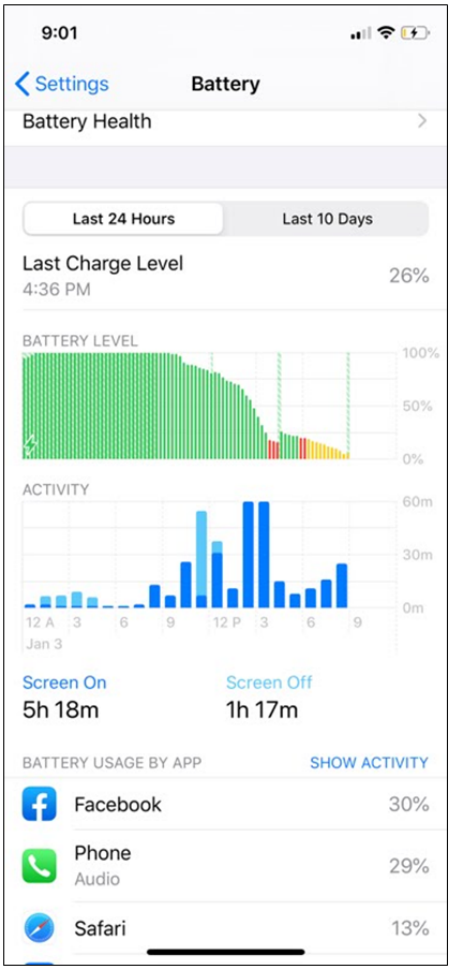
Passive Mobile Sensing (Screen Time Monitoring)

iOS Devices

Caregivers with an iPhone are texted with an automated reminder to send a screenshot of their screen time use each day at 9 PM to a study-specific phone number. The relevant information is located under the “Battery” tab in the iPhone settings. Figure 2 presents an example screenshot. Participants

send the research staff 1 practice screenshot (those with iOS devices) before the start of data collection. Trained research staff verify that the iOS screenshot contains the correct information and provide personalized feedback to the participants as needed. If a caregiver fails to send a correct screenshot during the 7 days of EMAs, the study staff send a personalized SMS text message within 24 hours. After the 7-day EMA period, the study staff send a personalized SMS text message if a caregiver fails to send a screenshot on 2 consecutive days (48 h).

Figure 2. Example screenshot to objectively measure screen time on a participants' iPhone.



Android Devices

Caregivers with an Android device are provided instructions to enroll in Chronicle, an app designed specifically for passive screen time monitoring on Android devices [18]. Chronicle collects and transmits the timestamped app use data automatically to its platform. During the 30-day monitoring period, the research staff monitor the Chronicle dashboard daily to ensure regular uploading of the screen time monitoring data. If more than 48 hours has lapsed since the last data uploaded from an active participant, the research staff contact caregivers to troubleshoot and then contact Chronicle support staff as necessary. The use of technical support (participant use of research staff technical support, as well as research staff requests from Chronicle support staff) are recorded as a feasibility outcome.

As caregiver smartphones are monitored, we will use a coding scheme to identify which apps are likely to be used by caregivers versus their children [16]. Two independent coders will categorize each app as either a child or an adult app based on information from the Apple and Google Play app stores; a third coder will arbitrate disagreements. During the qualitative interviews, caregivers are queried about whether their most frequently used apps are primarily used by themselves or their child.

Child Devices

Caregivers whose children have a compatible device (iOS or Android) are invited to enroll their child's device in the study using the same procedures as those used to enroll parents' devices. However, child device enrollment is not a requirement for the study.

Accelerometry

Both caregivers and children are asked to wear an Axivity AX3 (Axivity Ltd), a waterproof triaxial accelerometer, on their nondominant wrist for 30 days to assess physical activity, sedentary behavior, and sleep. The nondominant wrist placement improves compliance (compared with waist placement) [55]. Before data collection, the accelerometers are initialized using Open Movement (OMGui, version 1.0.0.43; Newcastle University) at a sample rate of 50 Hz with a range of +8*g* to −8*g*. Participants are mailed their accelerometers with reminders

about wearing the device, a sticker chart for children to track the number of days worn, and a prestamped envelope to return the accelerometers following the 30-day protocol. The participants are instructed to wear the device at all times, including sleeping periods. In the event of a lost or damaged device, a replacement device is mailed to the participant. The number of lost or damaged devices is used to determine the utility and feasibility of deploying accelerometers over longer wear periods (ie, 30 days).

Data Processing

Axivity data are downloaded using Open Movement (OMGui, version 1.0.0.43; Newcastle University). Raw Axivity AX3 .cwa accelerometer files are processed in R (R Foundation for Statistical Computing) using the GGIR package (version 2.6-4) [56]. During processing, GGIR autocalibrates the signal using local gravity as a reference, identifies abnormally high values, detects nonwear periods, and calculates the magnitude of the acceleration corrected for gravity. Files are excluded if the postcalibration error is >0.02*g* (a measure of acceleration) and if the wear time is less than 16 hours during the 24-hour period. The nonwear time is determined based on the SD and the value range of each accelerometer axes raw data during 15-minute blocks within a 60-minute window. These blocks are classified as nonwear time if the SD of the 60-minute window is <13 milli-g, and the value range of the 60-minute window is <50 milli-g for 2 of the 3 accelerometer axes [57]. The default method for nonwear time is used, as the average acceleration at similar times on days of the week is imputed for invalid data. We determine the time spent in physical activity intensity categories (eg, inactive, light, and moderate to vigorous) using the intensity thresholds (milli-g) described by Roscoe et al [58] and Hildebrand et al [59,60] for preschoolers and caregivers, respectively. Sleep outcomes are estimated using methods developed by van Hees et al [61], which identify periods of sustained inactivity when the z-angle does not change by >5° for at least 5 minutes.

Qualitative Interview

Following the 30-day monitoring period, caregivers are contacted by phone to complete a semistructured interview with a member of the research team (Multimedia Appendix 1). The semistructured interview is designed to address the following constructs of the study protocol: relevance, comprehensiveness, comprehensibility, satisfaction, and frequency or rationale of nonadherence [62-65]. Feedback provided by caregivers during the semistructured interviews is used to inform protocol changes for the future iterations of the study.

Compensation

In total, caregivers will receive up to US $180 in Amazon gift cards for participating in each wave of the study. Participants will be compensated with electronic gift cards that are delivered after they complete each study task. Caregivers will receive a US $15 gift card for completing the baseline survey. Caregivers who complete at least 21 EMA prompts (75%) will be considered compliant and receive a US $40 gift card. Participants who fail to complete 21 EMA prompts within the 7-day period will be given the option to extend their EMA period beyond 7 days to have additional survey opportunities. Those who complete 21 EMA prompts with additional days of surveys will be compensated the full amount (US $40). Caregivers will receive a US $30 gift card for completing at least 21 days (70%) of screen time monitoring on their smartphones. Caregivers will receive a US $50 gift card upon the return of the Axivity accelerometers; caregiver-child dyads who both wear the Axivity accelerometers for at least 21 valid days (70%) will receive an additional US $25 gift card. Finally, caregivers will be compensated US $20 for completing the semistructured phone interview.

Wave 2

A total of 50% (50/100) of the families who complete the study protocol will be invited to participate in a second wave of data collection 3 to 12 months after their initial enrollment. The 9-month discrepancy in the timing of the second wave is due to rolling recruitment. The purpose of the second wave of data collection is to evaluate the feasibility of retaining the sample over time and to assess the longer-term acceptability of the protocol. The protocol will be deemed feasible and acceptable if 80% of those invited agree to re-enroll in wave 2 of the study. Furthermore, the wave 2 protocol will be adapted based on wave 1 participant feedback.

Statistical Analyses

Data will be analyzed using IBM SPSS Statistics for Windows version 27. The descriptive statistics of the feasibility outcomes will be presented. As feasibility is the primary outcome of interest, we will use standard effect size estimates (ie, Cohen *d* and *r*) and minimal acceptable feasibility metrics in favor of significance testing [66]. Two-tailed independent sample *t* tests will be used to examine the differences between those who withdraw from the study and those who complete the protocol.

Sample Size

A sample size of 100 is adequate to evaluate the feasibility of the multibehavior protocol to measure digital media use and screen time context among preschoolers and their families, allowing for generalization to other families with children of similar age and demographics. Given that this is a pilot study, no power analysis is required [67].

Ethics Approval

The study protocol was approved by the institutional review board of the University of South Carolina (Approval Number: Pro00092634).

Results

The Tots and Tech study was funded in March 2020. Data collection began in September 2020 and was completed in May 2022. We aim to enroll 100 caregiver-child dyads. The Tots and Tech outcome paper is expected to be published in 2022.

Discussion

Overview

Excessive screen time has been linked to poor physical health outcomes (ie, obesity) [68] and mental health outcomes (ie,

attention-deficit/hyperactivity disorder and externalizing behaviors) [69,70]. However, studies evaluating the relationship between screen time and health behaviors have significant limitations. The existing studies on screen time have focused on television viewing, largely neglected digital media use [71], relied on retrospective parental reports of average screen time [12], and not yet examined individual variability or temporality [72] of screen time within a day. This study protocol is designed to address these weaknesses by (1) leveraging data already collected by smartphones and tablets (ie, app use) to objectively measure smartphone screen time and (2) integrating intensive longitudinal data collected from multiple sources (ie, passive mobile screen time sensing, EMA, and accelerometry).

This protocol attempts to overcome the methodological limitations of previous studies by incorporating objective measures of mobile screen time and health behaviors (physical activity, sedentary time, and sleep) in conjunction with EMA. The intention of this protocol is to measure screen time behaviors among caregivers and their preschool-age children more accurately. The results will be used to evaluate the feasibility and utility of a comprehensive multibehavior protocol to measure digital media use and screen time context. If this protocol is deemed feasible and acceptable, it can be used in future observational and intervention studies to better measure screen time and its context. In addition, this protocol makes it possible to examine more complex predictors of child health behaviors, such as the within-dyad daily dynamics and between-dyad associations between parenting practices and child behavior problems.

However, our methodology is not without limitations. Objectively monitoring mobile devices (eg, smartphones and tablets) can only provide objective information on digital media use, which is only one of the sources of screen time. It is likely that children and their caregivers also use other types of screen media (ie, television viewing, computers, and shared tablets). This additional screen use is assessed using a combination of EMA measures and traditional questionnaire data. Although the use of parent-report measures of children's additional screen time is less than ideal, the EMA method of intermittent assessment could reduce the recall bias present in many existing measures of *typical* screen use. Using this EMA method of screen assessment can provide temporal context to examine the within-day variability of screen time patterns. Future studies could leverage the emerging advances in facial recognition and machine-learning technology to passively and objectively measure additional forms of screen use among families.

The current methods of smartphone-based digital media–use assessment are also limited by the inability to determine who is using the smartphone. We attempt to disentangle smartphone use by determining whether the apps used are designed for children or adults. During qualitative interviews, caregivers indicate whether frequently used apps are used by themselves or by their children and provide information about who has access to the smartphone during peak time windows.

For the purpose of this feasibility study, all device use is considered screen time. However, the protocol for monitoring screen time on Android (but not iOS) devices provides information on how the device is being used (eg, app use) at specific times throughout the measurement period. Future studies can use this protocol to evaluate the differential effects of different types of screen time. For example, do children exhibit more behavioral problems following playing games on their tablet compared to video chatting? These studies are needed to advance science and inform guidelines for children's screen time.

To avoid overlapping time points and minimize missing data due to noncompliance [43], participants are sent 4 EMAs per day; these EMAs do not assess every hour of the day and, therefore, likely miss important screen time context and resultant child behaviors. Nevertheless, the methodology used by the Tots and Tech study greatly improves upon common methods in child screen time literature.

Conclusions

This study is designed to evaluate the feasibility and utility of a comprehensive multibehavior protocol to measure digital media use and screen time context among a racially and economically diverse sample of preschoolers and their families. The findings will inform protocol adjustments in preparation for a future well-powered study. Ultimately, the Tots and Tech study aims to reveal the process-oriented science that underlies the association between screen time and physical (ie, sleep and activity) and mental health (ie, behavioral problems). Preliminary data from this study will inform model convergence statistics and provide informative priors for the intraclass correlation coefficient and path estimates. These are necessary to conduct a power analysis to inform a future well-powered observational cohort study to examine these connections in further detail over time. The study protocol uses EMAs and objectively measured methods that can reveal the temporal mechanisms of health behavior. Understanding individual-level behavioral patterns has the potential to advance the science of personalized intervention approaches and inform health behavior theories to improve the health and well-being of children and their families.

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Data Availability

Data sharing is not applicable to this study, as no data sets were generated or analyzed during the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tots and Tech qualitative interview guide.
[DOCX File , 26 KB - resprot_v11i9e36240_app1.docx]

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Abbreviations

EMA: ecological momentary assessment

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Protocol

Investigating Recovery After Subarachnoid Hemorrhage With the Imaging, Cognition and Outcome of Neuropsychological Functioning After Subarachnoid Hemorrhage (ICONS) Study: Protocol for a Longitudinal, Prospective Cohort Study

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Abstract

Background: A subarachnoid hemorrhage is a hemorrhage in the subarachnoid space that is often caused by the rupture of an aneurysm. Patients who survive a subarachnoid hemorrhage have a high risk of complications and a negative long-term outcome.

Objective: The aim of the Imaging, Cognition and Outcome of Neuropsychological functioning after Subarachnoid hemorrhage (ICONS) study is to investigate whether and to what extent deficits exist in multiple domains after subarachnoid hemorrhage, including cognition, emotion and behavior, and to investigate whether brain damage can be detected in patients with subarachnoid hemorrhage. We aim to determine which early measures of cognition, emotion and behavior, and brain damage in the subacute stage play a role in long-term recovery after subarachnoid hemorrhage. Recovery is defined as functioning at a societal participation level, with a focus on resuming and maintaining work, leisure activities, and social relationships over the long term.

Methods: The ICONS study is an observational, prospective, single-center cohort study. The study includes patients with subarachnoid hemorrhage admitted to the Neurosurgery Unit of the University Medical Centre Groningen in the Netherlands. The inclusion criteria include diagnosis of an aneurysmal subarachnoid hemorrhage or an angiographically negative subarachnoid hemorrhage, sufficient ability in the Dutch language, and age older than 18 years. Patients will undergo neuropsychological assessment and magnetic resonance imaging 6 months after the subarachnoid hemorrhage. Furthermore, patients will be asked to fill in questionnaires on multiple psychosocial measures and undergo a structured interview at 6 months, 1 year, and 2 years after the subarachnoid hemorrhage. The primary outcome measure of the ICONS study is societal participation 1 year after the subarachnoid hemorrhage, measured with the Dutch version of the Impact on Participation and Autonomy questionnaire.

Results: The study was launched in December 2019 and recruitment is expected to continue until June 2023. At the time of the acceptance of this paper, 76 patients and 69 healthy controls have been included. The first results are expected in early 2023.

Conclusions: The ICONS study is the first to collect and combine data after subarachnoid hemorrhage in a variety of domains, including cognition, emotion and behavior, and brain damage. The results will contribute to a more comprehensive understanding of the consequences of both aneurysmal subarachnoid hemorrhage and angiographically negative subarachnoid hemorrhage,

which may ultimately optimize timely treatment for this patient group by setting realistic and attainable goals to improve daily functioning.

Trial Registration: Netherlands Trial Register NL7803; https://trialsearch.who.int/Trial2.aspx?TrialID=NL7803

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KEYWORDS

subarachnoid haemorrhage; cognition; neuroimaging; emotion and behavior; neuropsychology; longitudinal study; protocol; cohort study; bleeding; rupture; aneurysm; emotional; behavioral; brain damage

Introduction

Background

A subarachnoid hemorrhage (SAH) is a hemorrhage in the subarachnoid space, which is located between the pia mater and the arachnoid mater. In 75% to 80% of cases, a SAH is caused by a ruptured intracranial aneurysm; this is termed an aneurysmal SAH (aSAH). In approximately 15% of cases, no structural cause for the hemorrhage can be detected; this is defined as an angiographically negative SAH (anSAH). Despite the fact that SAH only accounts for 3% to 5% of all strokes, it has the highest morbidity and mortality rates of all stroke types [1]. One of the main clinical characteristics of SAH is an extremely severe headache with an acute onset. Half of all patients experience a loss of consciousness at onset [2]. Other symptoms include nausea, vomiting, neck stiffness, and focal neurological deficits. The main complications that may occur are acute hydrocephalus, recurrent hemorrhage, and cerebral vasospasm [3].

A distinctive feature of SAH is the relatively young age at which it occurs, with a peak incidence between 40 and 60 years [4]. Although recovery of functional independence is common, many SAH patients still experience negative long-term effects in everyday life functioning, which has a large impact on both patients and relatives. For example, previous studies have shown that more than 50% of all SAH patients are unable to resume their previous work, even in the absence of physical limitations [5,6]. In addition, many patients experience problems in leisure activities and social contacts after SAH [7,8]. Factors such as cognitive complaints, mood disorders, and behavioral deficits are related to these problems.

Cognitive and Emotional/Behavioral Consequences

After aSAH, disorders arise in both basic cognitive functions (such as memory, attention, and language) and higher-order functions (such as executive functions and social cognition) [5,9]. Even patients who are functionally independent (ie, able to perform activities of daily living without help) can experience cognitive impairment, causing disability in patients for months or even years after aSAH [7,10]. In addition, high rates of residual symptoms have been reported after aSAH, predominantly including fatigue, anxiety, and mood disturbances. These persistent cognitive and emotional sequelae may have a significant impact on the social and work life of patients. Previous studies have found that approximately 40% of aSAH patients are not able to return to their previous work between 1 to 4 years after ictus [6,11-13]. This can lead to reduced quality of life (QoL) in this patient group [14,15].

Cognitive outcomes following anSAH have been less well studied, and the existing literature shows contradictory results. While some studies have not found evidence of cognitive deficits in this patient group, others have found lower scores for divided attention, information processing speed, and memory [16-18]. A recent systematic review by Burke and colleagues [19] implied that a diffuse pattern of cognitive impairments can be seen in anSAH patients, with primarily attention and executive functioning being affected. Moreover, subjective complaints related to cognitive functioning, fatigue, and mood have been steadily reported after anSAH and seem to significantly influence QoL [16,20-22].

Furthermore, both aSAH and anSAH patients show changes in behavior and personality, such as apathy [23] and inadequate social behavior [24-26]. Changes in behavior are often accompanied by impaired self-awareness [27]. This casts doubt on whether self-reported measures alone can be used to assess the presence and frequency of long-term consequences of SAH and emphasizes the importance of obtaining measures from informants. Although cognitive, emotional, and behavioral deficits after SAH have been frequently explored, the explanatory value of these domains for long-term recovery in the subacute stage after SAH has not yet been investigated.

Brain Damage After SAH

SAH may result in diffuse injury caused by the initial hemorrhage, complications (eg, vasospasms, hydrocephalus, and recurrent hemorrhage), or secondary damage due to delayed cerebral ischemia. Treatment of the aneurysm in the case of aSAH generally involves either microsurgical occlusion (clipping) or endovascular obliteration (coiling, stenting, or both). Previous studies have investigated the effects of clinical parameters (eg, the characteristics of the aneurysm, the treatment modality, vasospasm, and cerebrospinal fluid drainage) on outcomes after SAH. However, no clear evidence for the effects of these parameters has been found. For example, in a study of 32 aSAH patients, no association was found between the site of the aneurysm or the mode of treatment with neuropsychological outcomes [28]. The authors did find that the severity of the hemorrhage was significantly linked with intelligence and memory. Another study, which included 23 aSAH patients who underwent coiling or clipping, found no differences in cognitive outcomes with different treatment modalities [29]. The aneurysm location also did not seem to be related to the resumption of social activities in a group of 200

aSAH patients [7]. It is therefore of great importance to take a more in-depth look into the diffuse brain damage that may occur after SAH.

Brain imaging techniques, such as magnetic resonance imaging (MRI), can identify structural changes after SAH. For example, T2-weighted, fluid-attenuated inversion recovery and 3D T1-weighted images can depict a variety of etiologies, such as ischemic lesions and brain abnormalities that can be the result of aneurysm treatment (either microsurgical or endovascular), lesions associated with external ventricular drains or permanent shunt placement, and previous infarctions [30]. A recent study obtained complete T1-weighted data 3 months post-aSAH and found no difference in total gray-matter or white-matter volume between patients and controls [31]. However, that study did find a significantly higher gray-matter volume in the cerebellum of aSAH patients than controls, and the study also found an association with neurocognitive impairment.

There are some promising imaging techniques that have not been used, or have barely been used, in the SAH patient population; these techniques have the potential to contribute to knowledge about the long-term cognitive consequences of SAH. First, diffusion tensor imaging (DTI) can identify microstructural white matter lesions that are not visible with standard brain MRI [32]. The most-examined parameters in DTI studies are fractional anisotropy (FA), mean diffusivity (MD), and apparent diffusion coefficient (ADC). Previous research has shown that 2 weeks after ictus, aSAH patients have higher MD values than patients with an unruptured intracranial aneurysm [33]. Higher MD values were associated with cognitive impairment 3 months after ictus in these patients. Another study found decreased FA in the corpus callosum and increased ADC values in the frontal centrum semiovale in aSAH patients 8 to 10 days after ictus [34]. To date, DTI has not been used in anSAH patients, and it is therefore unknown to what extent damage in the white-matter microstructure relates to less favorable cognitive outcomes in this patient group and whether this differs between aSAH and anSAH patients. A more advanced and promising technique is diffusion kurtosis imaging (DKI). DKI has the potential to further delineate microstructural aspects of the white matter [35] and has been used in the assessment and differentiation of stroke, brain tumor, and neurodegenerative diseases [36,37]. To our knowledge, DKI has not yet been used in SAH patients. Second, arterial spin labeling data can be used to measure blood flow in brain tissue (ie, perfusion) and has demonstrated clinical usefulness in various diseases, including vascular spasm, brain tumors, and Alzheimer disease [38-40]. Third, susceptibility weighted imaging (SWI), a relatively new tool for imaging blood vessels, hemorrhage, iron and blood products, and calcifications [41,42], has been used to detect parenchymal hemorrhage and can detect small amounts of SAH more sensitively than conventional gradient-echo sequences [43]. SWI data can be used as input for quantitative susceptibility mapping (QSM.) QSM is a novel MRI technique that has been used to study brain iron and blood degeneration products in various patient populations, such as those with traumatic brain injury, brain tumors, or neurodegenerative diseases [44]. QSM has the potential to indicate hemorrhages and microhemorrhages in a more accurate and qualitative way than SWI in a variety of neuropathologies [45]. Fourth, vessel architectural imaging (VAI) is a new dual-echo dynamic susceptibility contrast (DSC) perfusion sequence technique that can reveal the microvascular architecture and oxygen saturation status. To date, VAI has only been used in tumor patients and has been shown to provide better insights than other noninvasive imaging techniques into the complex nature and heterogeneity of vascular changes [46,47]. In addition, single-echo DSC can be used to gain a better understanding of heterogeneity in microvascular and capillary transit time and the oxygen extraction fraction [48]. Finally, synthetic MRI is a technique whereby a single scan can be used to create multiple different contrast-weighted snapshots, allowing automatic brain segmentation and myelin volumetric measurements [49]. In short, the above MRI methods may allow the evaluation of brain damage after SAH, particularly vascular damage, in a more comprehensive and sensitive way. Moreover, the application of these techniques may offer important new insights into the brain damage that underlies cognitive impairment and difficulties in daily functioning after SAH.

Objectives

The overall aims of the Imaging, Cognition and Outcome of Neuropsychological functioning after Subarachnoid hemorrhage (ICONS) study are to determine whether and to what extent there are deficits in multiple domains after SAH (including cognition, emotion, and behavior) and to investigate whether brain damage can be detected in this patient group. If this is the case, we aim to determine which early measures (including measures of cognition, emotion and behavior, and brain damage) in the subacute stage play a role in long-term recovery after SAH. Recovery is defined as societal participation, focusing on resuming and maintaining work, leisure activities, and social relationships over the long term. Furthermore, the study has 12 specific objectives that focus on the domains of cognition, emotion and behavior, and brain damage, which will be targeted in multiple future papers. These objectives are described in Textbox 1. We expect that all studied measures will have an effect on recovery individually, but that in an overall explanatory model the neuropsychological factors will play a more decisive role than the initial brain damage. Early identification of decisive factors may provide target points for rehabilitation in this patient group.

Textbox 1. Objectives of the Imaging, Cognition and Outcome of Neuropsychological Functioning After Subarachnoid Hemorrhage (ICONS) study.

Overall aims

We aim to determine whether and to what extent deficits exist after subarachnoid hemorrhage in multiple domains, including cognition, emotion, and behavior, and to investigate whether brain damage can be detected in patients with subarachnoid hemorrhage. We also aim to determine which early measures of cognition, emotion and behavior, and brain damage in the subacute stage play a role in long-term recovery 1 year after subarachnoid hemorrhage.

Aims in the cognition domain

1. Determine whether and to what extent there are deficits in various cognitive domains (eg, executive functioning, language, memory, processing speed, social cognition, and visuoconstructive skills) 6 months after subarachnoid hemorrhage
2. Investigate whether and to what extent there are relationships between cognitive functioning 6 months after subarachnoid hemorrhage and individual patient characteristics (eg, age, treatment, type of subarachnoid hemorrhage, severity of subarachnoid hemorrhage, and complications)
3. Investigate whether and to what extent there are relationships between cognitive functioning 6 months after subarachnoid hemorrhage and emotional and behavioral characteristics (eg, anxiety, mood complaints, fatigue, and posttraumatic stress) 1 and 2 years after subarachnoid hemorrhage
4. Investigate the relationship between cognitive functioning 6 months after subarachnoid hemorrhage and recovery 1 and 2 years after subarachnoid hemorrhage

Aims in the emotion and behavior domain

1. Determine emotional and behavioral consequences in various domains (eg, anxiety, mood complaints, fatigue, subjective cognitive complaints, posttraumatic stress, and quality of life) 6 months after subarachnoid hemorrhage
2. Investigate whether and to what extent there are relationships between emotional and behavioral consequences and individual patient characteristics (eg, age, treatment, type of subarachnoid hemorrhage, severity of subarachnoid hemorrhage, and complications)
3. Determine the improvement of emotional and behavioral consequences over time, as measured at 6 months, 1 year, and 2 years after subarachnoid hemorrhage
4. Investigate the relationship between emotional and behavioral consequences 6 months after subarachnoid hemorrhage and recovery 1 year and 2 years after subarachnoid hemorrhage

Aims in the brain damage domain

1. Determine differences in brain tissue between patients and matched healthy controls using advanced imaging techniques
2. Determine differences in brain tissue between patients with aneurysmal subarachnoid hemorrhage and angiographically negative subarachnoid hemorrhage using advanced imaging techniques
3. Investigate the relationship between impairments in cognitive domains (eg, executive functioning, language, memory, processing speed, social cognition, and visuoconstructive skills) and specific lesion patterns as identified with advanced imaging techniques
4. Investigate the relationship between brain damage 6 months after subarachnoid hemorrhage and recovery 1 year and 2 years after subarachnoid hemorrhage

Methods

Study Design

The ICONS study is a longitudinal, prospective, single-center cohort study that aims to include 150 patients with SAH who will be followed up at 6 months, 1 year, and 2 years after ictus.

Study Population

Patients are being recruited from the Neurosurgery Unit of the University Medical Centre Groningen (UMCG), the Netherlands. Based on the admission rate of approximately 120 patients with SAH per year at the UMCG, and accounting for unwillingness to participate and loss to follow-up, we aim to recruit 150 patients with SAH. In addition, 100 matched healthy controls will be recruited through convenience sampling. Inclusion criteria are an aSAH or anSAH diagnosis established by means of a computed tomography (CT) scan. The presence or absence of an intracranial aneurysm (ie, aSAH or anSAH, respectively) is evaluated using CT angiography, digital subtraction angiography, or both. Other inclusion criteria include sufficient knowledge of the Dutch language and age older than 18 years. Exclusion criteria for both patients and healthy controls are a poor physical condition that makes it impossible for participants to undergo the neuropsychological assessment or MRI scan and a history of severe neurological disorders.

Study Procedures

Patients

Data collection is administered and performed by 2 researchers (ie, neuropsychologists). The researchers inform patients about the study upon discharge from the hospital by handing them written information regarding the purpose and design of the study. Six weeks after SAH, patients have an outpatient check-up appointment with their treating physician. Following this appointment, patients have the opportunity to speak with the researchers and pose questions about the study. Written informed consent is then obtained. Patients who do not consent

to the study receive standard clinical aftercare according to the UMCG SAH protocol.

After informed consent is obtained, demographic and medical data are obtained from patients' medical records, including the World Federation of Neurological Surgeons (WFNS) grade. The WFNS grading scale is the most-used classification method for determining the initial clinical condition after SAH and is based on loss of consciousness; it ranges from 1 to 5 [50]. The researchers schedule the neuropsychological assessment (NPA) and MRI scan on 2 separate days, approximately 6 months post-SAH. The maximum time between the MRI and the NPA is 1 month. The MRI scan takes approximately 1 hour (a 50-minute scan time and 10-minute preparation time).

Patients receive questionnaires regarding emotion and behavior 2 weeks prior to the NPA (Table 1). These questionnaires are sent digitally via the secure web app Research Electronic Data Capture (REDCap) or, upon request, on paper. At the NPA appointment, the investigator scrutinizes the questionnaires (eg, checks for missing data or questions with multiple answers selected). The NPA takes approximately 3 hours and consists of a structured interview with the patient and a neuropsychological test battery covering different cognitive domains (Table 1). During the interview, the researchers document the patient's level of education, their handedness, and their self-reported cognitive, emotional, and behavioral complaints. Furthermore, a questionnaire regarding the patient's sleep patterns, resumption of work, and the type and amount of any previously received rehabilitation or psychological treatment is administered. We expect the duration of the NPA to be feasible, because a previously conducted study with SAH patients made use of a more-extensive neuropsychological test battery that was shown to be feasible for this patient group [11]. However, if needed, the patients are allowed small breaks during the NPA, and if necessary, the appointment can also be divided over 2 days. Patients receive follow-up assessments 1 year and 2 years post-SAH. For the 1-year follow-up, the researchers schedule an appointment with the patient at the UMCG. The 2-year follow-up assessment is a telephone interview. The patients receive the questionnaires 2 weeks before each follow-up assessment.

Table 1. Overview of the assessments used for the Imaging, Cognition and Outcome of Neuropsychological functioning after Subarachnoid hemorrhage (ICONS) study.

Assessments	Construct	Six-month follow up	One-year follow up	Two-year follow up
General information (patients)				
Demographics	Age, sex, education	✓		
Medical data	Treatment, SAH[a] type, aneurysm, complications	✓		
Modified Rankin Scale	Functional status	✓	✓	✓
Sleep-work-treatment questionnaire	Brain structural changes	✓	✓	✓
Neuropsychological tests (patients)				
Rey Complex Figure Test copy	Visuospatial construction	✓		
15 Words Test	Verbal memory	✓		
Digit Span Test of the Wechsler Adult Intelligence Scale IV	Memory span/working memory	✓		
Letter Fluency test	Executive functioning	✓		
Zoo Map Test of the Behavioural Assessment of the Dysexecutive Syndrome	Executive functioning	✓		
Key Search Test of the Behavioural Assessment of the Dysexecutive Syndrome	Executive functioning	✓		
Trail making test	Complex attention	✓		
Vienna Test System reaction time test	Complex attention	✓		
Semantic Fluency test	Language	✓		
Hinting Task	Social cognition	✓		
Cartoons test	Social cognition	✓		
Facial expression of emotion: stimuli and tests	Social cognition	✓		
Dutch Adult Reading Test	Premorbid intelligence	✓		
Questionnaires (patients)				
Impact on Participation and Autonomy	Participation		✓	✓
Utrecht Scale for Evaluation of Rehabilitation	Participation activities	✓	✓	✓
Checklist for cognitive and emotional consequences following stroke	Cognitive and emotional complaints	✓	✓	✓
Dysexecutive questionnaire	Dysexecutive syndrome	✓	✓	✓
Dutch Multifactor Fatigue Scale	Fatigue	✓	✓	✓
Hospital Anxiety and Depression Scale	Anxiety and depression	✓	✓	✓
Life Satisfaction Questionnaire	Quality of life	✓	✓	✓
Impact of Events Scale	PTSD[b]	✓	✓	✓
Utrecht Coping List	Coping	✓		
Questionnaires (proxies)				
Utrecht Scale for Evaluation of Rehabilitation	Participation activities	✓	✓	✓
Checklist for cognitive and emotional consequences following stroke	Cognitive and emotional complaints	✓	✓	✓
Dysexecutive questionnaire	Dysexecutive syndrome	✓	✓	✓
Socioemotional Dysfunction Scale	Social dysfunction	✓	✓	✓
MRI[c] brain scanning (patients)				
3D-T1 MRI	Brain structural changes	✓		
T2 MRI	Brain structural changes	✓		

Assessments	Construct	Six-month follow up	One-year follow up	Two-year follow up
Fluid attenuated inversion recovery	Brain segmentation	✓		
Synthetic MRI	Myelin volumetric measurements	✓		
Diffusion kurtosis imaging/diffusion tensor imaging	Microstructural white matter lesions	✓		
Arterial spin labeling	Perfusion parameters	✓		
Vessel architectural imaging	Microvascular architecture	✓		
Susceptibility weighted imaging/quantitative susceptibility mapping	(Micro)hemorrhagic damage	✓		

[a]SAH: subarachnoid hemorrhage.

[b]PTSD: posttraumatic stress disorder.

[c]MRI: magnetic resonance imaging.

Proxies

Patients are requested to bring a proxy (eg, a significant other or close relative) to the NPA. These proxies are asked to fill out several questionnaires (Table 1). Additionally, a checklist of cognitive and emotional consequences following stroke is filled out during a short individual interview. Informed consent is obtained from the proxy before study participation. Like the patients, they fill out online (or paper, upon request) questionnaires at the 1-year and 2-year follow-ups.

Healthy Controls

A total of 100 healthy controls will be included for the NPA, of which 30 will undergo an MRI scan. Subjects are first included for the NPA and afterwards asked whether they are also willing to undergo an MRI scan. The MRI protocol for the healthy controls is the same as for the patients. If an unexpected abnormality is found on the MRI scan, the general practitioner of the healthy control will be contacted. The healthy controls give permission for this procedure when signing the informed consent form. The test battery of the NPA is the same as for the patients, but the structured interview and proxy measures are excluded. The healthy control group will be matched for age, gender, and education using frequency matching.

Data Collection Instruments

Impact on Participation and Autonomy

The primary outcome measure of the ICONS study will be the Dutch version of the Impact on Participation and Autonomy (IPA) [51] scale, assessed 1 year after the SAH via a structured interview. The IPA scale has been developed to assess problems experienced by patients regarding autonomy and participation. The questionnaire contains a total of 41 items, each scored on a 5-point rating scale with the following labels: 0 (very good), 1 (good), 2 (fair), 3 (poor), and 4 (very poor). The items are divided into 5 domains, of which the following 3 will be used in the ICONS study: family role (7 items), social relationships (7 items), and work and education (6 items). The total score is calculated by summing up these 3 domains and ranges from 0 to 80. Since these domains measure data at an ordinal level, the results will be dichotomized into “complete recovery of societal participation” (for scores from 0-20) and “incomplete recovery of societal participation” (for scores 21-80) to perform logistic regression analyses.

Neuropsychological Assessment

Table 1 lists the cognitive domains and the associated neuropsychological tests that will be used. All tests are commonly used in both research and clinical practice within the Netherlands and have either normative data or data from healthy controls available. To control for insufficient effort of participants, we will use embedded indicators, such as the 15 Words Test and the Digit Span Task. Performance of the patients will be compared with that of the healthy controls. Raw test results will be converted into relevant statistics (eg, *z* scores, *t* scores, or percentiles), by using normative scores for standard neuropsychological tests.

Questionnaires

Questionnaires regarding emotional and behavioral disturbances are administered 6 months, 1 year, and 2 years after SAH to investigate how patients recover over time (Table 1).

Magnetic Resonance Imaging

MRI data are acquired on a 3-tesla scanner (Magnetom Prisma, Siemens) with a standard 64-channel head coil. A standardized scanning protocol is used. The MRI sequences are listed in Table 1. The MRI data will be analyzed and processed with various software packages, such as the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) [52], the voxel-based morphometry (VBM) toolbox under statistical parametric mapping (Wellcome Department of Imaging Neuroscience), and the cNeuro image quantification Conformité Européenne-marked tool (Combinostics Ltd). The FSL is a comprehensive library of analysis tools for functional MRI and DTI brain imaging data. VBM is an automated technique for the analysis of neuroanatomical images that identifies regional differences in gray matter and white matter between groups of subjects without a prior region of interest. cNeuro provides fully automated brain MRI quantification. Perfusion data will be analyzed using a research version of Nordic (NordicNeuroLab) and a research version of Cercare Medical Neurosuite (Cercare Medical).

Data Management

The data are stored in an electronic case report form (eCRF) using REDCap. Imaging data are stored on a local secured server at the UMCG. Metadata are stored in the eCRF. Study monitoring is performed by in-house study monitors from the UMCG. Since our data contain potentially sensitive information and therefore pose privacy concerns (even when anonymized), there will be ethical restrictions on sharing our data set. Restrictions will be imposed by the Medical Ethical Committee of the UMCG.

Statistical Analysis

Descriptive statistics (including frequencies, means, and 95% CIs) will be used to describe the samples, and data from each variable will be summarized separately for patients and healthy controls. Deficits in multiple domains will be determined by comparing patients with healthy controls (at the group level) and by comparing patients' scores with normative data (at the individual level). Test performance below the 10th percentile will be considered impaired. Statistical analyses will be performed according to the applicable objectives shown in Textbox 1. Furthermore, we will develop three explanatory models: (1) cognition, (2) emotion and behavior, and (3) brain damage; this will use binary logistic regression analyses with recovery (ie, IPA ≤20 or IPA ≥21) as the dependent variable. A significance of α=.05 will be used as the cut-off for each variable. Only variables that are expected to have a strong relationship with the dependent variable will be included, based on a priori expectations from the literature and clinical experience. Measures for the same cognitive domains (Table 1) will be taken together as a composite score. The composite score will be generated by converting raw test scores from individual measures to *z* scores and averaging them. Lastly, we will create an overall comprehensive explanatory model that takes into account the most sensitive measures from each domain (ie, cognition, emotion and behavior, and brain damage) to see how these measures relate to each other in explaining recovery 1 year after SAH.

Sample Size

In multivariable logistic regression models, a sample size of 10 events per variable (EPVs) is desirable to preserve the validity of the model [53]. This rule indicates that 1 independent variable can be studied for every 10 events. For logistic regression, the number of events is given by the smallest number of events within the 2 outcome categories. Based on previous literature, we expect that around half the patients (n=75) will have a complete recovery 1 year after SAH, while the other half (n=75) will have an incomplete recovery 1 year after SAH [7]. This implies that 7 (ie, 75 / 10 = 7.5) variables will be able to be reliably fitted to the model. However, in analyses of causal influences in observational data, control for confounding variables may require adjustment for more covariates than the rule of 10 EPVs allows. Vittinghof and McCullough [54] demonstrated that problems are fairly frequent with 2 to 4 EPVs, uncommon with 5 to 9 EPVs, and still observed with 10 to 16 EPVs when regarding CI coverage less than 93 percent, type 1 error larger than 7 percent, or relative bias larger than 15 percent as problematic. Following these findings, using 5 EPVs will allow for 15 (ie, 75 / 5 = 15) independent variables in each model.

Additionally, 100 healthy controls will be included in order to perform comparisons with the patient group and determine reference values. Since the ICONS study will use new neuroimaging methods, reference values will be needed to compare and interpret the MRI data. Healthy subjects show less variability in results than patients, which means that a smaller number of healthy subjects will be required. Previous MRI studies with SAH patients have shown that the number of healthy controls targeted in the ICONS study will be sufficient [55,56].

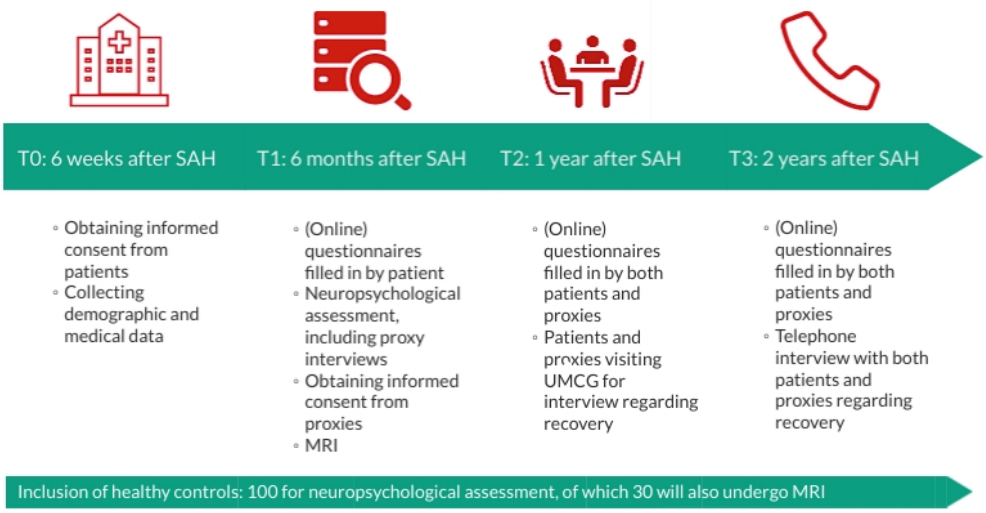
Ethics Approval and Consent to Participate

The ICONS study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and the national and international standards of Good Clinical Practice. Potential participants receive detailed written and oral information on the study procedures and all participants will provide written informed consent. Ethical approval of the study protocol was obtained from the Medical Ethical Committee of the UMCG (2019/346). The ICONS study protocol is registered at the Dutch Central Committee of Research Involving Human Subjects, with trial registration number NL69873.042.19. In addition, the study was registered on June 19th, 2019, at the Netherlands Trial Register with identifier NL7803.

Results

As of December 2019, we enrolled 76 patients and 69 healthy controls. Recruitment is planned to continue until June 2023. The first publications are expected in early 2023. An overview of the timeline and assessments of the ICONS study is depicted in Figure 1.

Figure 1. Timetable of the Imaging, Cognition and Outcome of Neuropsychological functioning after Subarachnoid hemorrhage (ICONS) study. MRI: magnetic resonance imaging; SAH: subarachnoid hemorrhage; UMCG: University Medical Centre Groningen.



Discussion

The ICONS study is the first to combine the domains of cognition, emotions and behavior, as well as the first to use MRI imaging biomarkers, to investigate recovery in a longitudinal cohort of SAH patients and to determine which domain plays the most decisive role in long-term recovery, and consequently find better targets for rehabilitation. We believe this study will add to the existing literature for several reasons.

First, the most commonly used scales to determine functional outcomes in SAH patients are the modified Rankin Scale (mRS) and the Glasgow Outcome Scale (GOS). However, previous research has shown that patients with a "good" outcome (ie, a GOS score of 1) may still have substantial cognitive impairments and emotional problems, which indicates that these scales are not sufficiently sensitive [57,58]. Additionally, a study of 214 aSAH patients showed that one-third of patients with an mRS score of 0 (ie, "no symptoms at all") were unable to return to work, and that 1 in 6 experienced mood disturbances [59]. The ICONS study measures outcome as functioning at a participation level, with a focus on both resuming and maintaining work, leisure activities, and social activities over the long term. This is especially important for patients with SAH, because SAH often occurs at a relatively young age, when patients are in a stage of life in which they generally have important tasks and responsibilities in their family, work, and social environment.

Second, whereas the vast majority of SAH research only focuses on aSAH patients, the current study also includes anSAH patients. In comparison to aSAH patients, clinical outcomes for anSAH patients are significantly better, including lower rates of delayed cerebral ischemia and radiologic infarction [60]. Therefore, anSAH is often considered a benign disorder. However, diffuse cognitive deficits have been demonstrated [19], and subjective complaints regarding cognition, fatigue, and mood are common [16,21,22]. The ICONS study will, furthermore, be the first to perform MRI imaging in anSAH patients. This will provide more knowledge into whether brain damage is the underlying cause of the problems experienced by this patient group.

Third, this is the first study to assess a variety of new and advanced neuroimaging methods in SAH patients. These techniques are more sensitive than conventional MRI (eg, for detecting cerebral microbleeds and vasospasm and their consequences in the brain). Their application may therefore offer important new insights into the brain damage underlying the cognitive disorders and difficulties in daily functioning after SAH.

A limitation of the study design is that only those patients who are able to undergo the NPA and MRI scans are included. Therefore, the results may not be applicable to more severely impaired SAH patients. Additionally, this is a single-center study, which might also affect the generalizability of the results.

In conclusion, the results of the ICONS study will contribute to a more comprehensive and timely understanding of the consequences of both aSAH and anSAH, which may ultimately allow the optimization of timely treatment for this patient group by setting realistic and attainable goals to improve daily functioning. Furthermore, based on the findings of this study, psychoeducation for patients and their families might be improved.

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Data Availability

Depending on the type of data and associated privacy regulations, data from the Imaging Cognition and Outcome of Neuropsychological Functioning After Subarachnoid Hemorrhage (ICONS) study will be made available upon reasonable request to the principal investigator (AMB).

Authors' Contributions

SK and LSJ were both equally involved in the conception, organization, and execution of the study, as well as writing the first draft of the manuscript and making later revisions. AMB was involved in the conception, organization, and execution of the study and reviewed the manuscript as the principal investigator. SER, MET, RJHB, AH, RJMG, and JMS were involved in the conception, organization, and execution of the study and reviewed the manuscript. This paper has not been previously published, nor is it under simultaneous consideration by any other journal. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADC: apparent diffusion coefficient
anSAH: angiographically negative subarachnoid hemorrhage
aSAH: aneurysmal subarachnoid hemorrhage
CT: computed tomography
DKI: diffusion kurtosis imaging
DSC: dynamic susceptibility contrast
DTI: diffusion tensor imaging
eCRF: electronic case report form
EPV: event per variable
FA: fractional anisotropy
FSL: FMRIB Software Library
GOS: Glasgow Outcome Scale
ICONS: Imaging, Cognition and Outcome of Neuropsychological functioning after Subarachnoid hemorrhage
IPA: Impact on Participation and Outcome
MD: mean diffusivity
MRI: magnetic resonance imaging
mRS: modified Rankin scale
NPA: neuropsychological assessment
QoL: quality of life
QSM: quantitative susceptibility mapping
SAH: subarachnoid hemorrhage
SWI: susceptibility weighted imaging
UMCG: University Medical Centre Groningen
VAI: vessel architectural imaging
VBM: voxel-based morphometry
WFNS: World Federation of Neurological Surgeons

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Protocol

The Influence of Context on Implementation and Improvement: Protocol for a Mixed Methods, Secondary Analyses Study

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Abstract

Background: Caring for the well-being of older adults is one of the greatest challenges in modern societies. Improving the quality of care and life for older adults and the work lives of their care providers calls for effective knowledge translation of evidence-based best practices.

Objective: This study's purpose is to contribute to knowledge translation by better understanding the roles of organizational context (workplace environment) and facilitation (process or role) in implementation and improvement success. Our study has 2 goals: (1) to advance knowledge translation science by further developing and testing the Promoting Action on Research Implementation in Health Services framework (which outlines how implementation relies on the interplay of context, facilitation, and evidence) and (2) to advance research by optimizing implementation success via tailoring of modifiable elements of organizational context and facilitation.

Methods: This is secondary analyses of 15 years of longitudinal data from the Translating Research in Elder Care (TREC) program's multiple data sources. This research is ongoing in long-term care (LTC) homes in western Canada. TREC data include the following: 5 waves of survey collection, 2 clinical trials, and regular ongoing outcome data for LTC residents. We will use a sequential exploratory and confirmatory mixed methods design. We will analyze qualitative and quantitative data holdings in an iterative process: (1) comprehensive reanalysis of qualitative data to derive hypotheses, (2) quantitative modeling to test hypotheses, and (3) action cycles to further refine and integrate qualitative and quantitative analyses. The research team includes 4 stakeholder panels: (1) system decision- and policy makers, (2) care home managers, (3) direct care staff, and (4) a citizen engagement group of people living with dementia and family members of LTC residents. A fifth group is our panel of external scientific advisors. Each panel will engage periodically, providing their perspectives on project direction and findings.

Results: This study is funded by the Canadian Institutes of Health Research. Ethics approval was obtained from the University of Alberta (Pro00096541). The results of the secondary analyses are expected by the end of 2023.

Conclusions: The project will advance knowledge translation science by deepening our understanding of the roles of context, the interactions between context and facilitation, and their influence on resident and staff quality outcomes. Importantly, findings will inform understanding of the mechanisms by which context and facilitation affect the success of implementation and offer insights into factors that influence the implementation success of interventions in nursing homes.

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KEYWORDS

organizational context; facilitation; PARIHS framework; Promoting Action on Research Implementation in Health Services; implementation science

Introduction

Background

Concerns about quality in long-term care (LTC) homes are not new—the literature overflows with decades of calls to improve quality of care in LTC [1-4]. International [3,5], national [6-9], and provincial [10-12] reports highlight the suboptimal quality of LTC. Effective programs for improving quality of care in LTC homes are available, but implementation of these evidence-based programs has had inconsistent success across studies [1,13]. Implementation success is a proximal outcome that should lead to more distal improvement in outcomes for resident care quality or staff quality of work life (improvement success). One key outcome indicating implementation success in health care settings is the uptake of best practices (also called best practice use or research use) by health care workers such as physicians, regulated nurses, and unregulated staff. Researchers have noted a persistent lack of success in implementing evidence-based programs and cite a lack of understanding of the interrelating factors influencing implementation as a major knowledge gap [14,15].

Theoretical Framing: the Promoting Action on Research Implementation in Health Services Framework

The Promoting Action on Research Implementation in Health Services (PARIHS) framework is widely used in implementation science [16-18] and offers a guide for implementing quality improvement programs in health care settings. This framework proposes that successful implementation of research evidence depends on the interplay of context, facilitation, and evidence [16-18]. In this study, we focus on two of the framework's key elements: context and facilitation. They have critical roles in influencing implementation and improvement success—and outcomes for residents and care staff.

The PARIHS definition of context is highly general: the setting where a proposed change is to be implemented [17]. PARIHS developers initially conceptualized context as including culture, leadership, and evaluation (feedback of data to end users). Researchers using the framework now acknowledge more components of context, generally divided into inner context (immediate local setting, the organization) and outer context [19,20] (health system of organization and policy, social, regulatory, and political infrastructures) [16]. Context is highly modifiable using strategies to improve service quality and outcomes [21-23] and is therefore vital to improvement initiatives [24,25]. Research increasingly emphasizes the central role of organizational context in the success of both implementation and improvement initiatives, and its influence on workforce and resident outcomes in LTC homes [24,26-31]. Accordingly, researchers increasingly focus on organizational context (context within the workforce) as a core element of quality improvement initiatives [15,32] and consider the influence of context on implementation [16,33].

Elements of context (eg, leadership, social capital, decision-making autonomy, and communication) are associated with outcomes for direct care staff in LTC homes, such as job satisfaction, burnout, use of best practices, and tasks rushed or left undone [26,27,34-39]. Context elements also influence quality of life and care for LTC residents [28]. Residents in LTC homes with a more favorable context had significantly lower burdensome symptoms (eg, pain, shortness of breath, and urinary tract infection) and lower use of antipsychotics without a diagnosis of psychosis [28]. A review of qualitative studies found that poor context (culture that is not collaborative, is hierarchical, or has leadership that is poorly connected with realities faced by staff) negatively affected performance (eg, quality of care) in health care organizations [40].

However, despite decades of work on context, no coherent body of evidence clearly demonstrates context conditions for success [14,24,25]. Work from this research team has provided early evidence of the influence of context on LTC staff and resident outcomes [28], but further research is needed to deepen our understanding of these relationships. With these studies, we can begin to understand the complex causal mechanisms and the necessary and sufficient context conditions that produce particular outcomes for implementation and improvement success.

Facilitation Influences Implementation and Improvement Success

The PARIHS framework considers a second component, facilitation, as both a role (eg, coach or educator) and a process (of enabling others) [41]. Emerging research highlights facilitation's critical role in implementation and improvement initiatives [42-48]. A 2012 systematic review found that primary care settings supported by a facilitator were 2.76 times more likely to adopt evidence-based clinical guidelines [49]. In our recent empirical work, we successfully improved the involvement of LTC care aides in formal communications [29,50]. We also used targeted facilitation interventions, with external quality experts supporting LTC managers to change context-of-care units using goal setting theory [29,50].

Despite these insights, a lack of theoretical grounding is one factor that continues to limit our understanding of the effects of facilitation on implementation success [46,48]. Theoretical analysis suggested that varied effectiveness of facilitation is related to factors that influence organizational learning, because facilitation acts as a learning mechanism [48]. Optimizing facilitation (within a given context) may amplify organizational

learning processes, making it easier to tailor facilitation to local context [47].

Context Elements and Facilitation Interact to Influence Implementation Success

The PARIHS framework suggests that context factors and facilitation interact in complex ways, but neither the PARIHS developers nor other researchers have addressed directionality, addressed mechanisms of interactions, or actively and empirically assessed wider context factors (Y Duan et al, unpublished data, forthcoming) [41,51]. Some evidence points to facilitation as a key ingredient in implementation initiatives, but only preliminary work in small-scale qualitative studies addresses the influence of interactions between facilitation and context [52]. In previous work, we used cross-sectional data and demonstrated that the association of leadership with use of best practices by LTC care staff was moderated by clinical educators—an internal facilitator role in LTC homes [30]. Further research is warranted for a deeper understanding of how and under what conditions do context and facilitation interact and how these interactions affect resident and care staff health and well-being.

Previous Work

Our integrated knowledge translation program, Translating Research in Elder Care [53] (TREC), was founded to focus on (1) contributing to knowledge translation or implementation science and (2) developing practical research-based solutions to improve LTC quality of care, life, and work life. Preceding this project, we (1) developed instruments that measure PARIHS constructs in LTC [54,55], (2) framed clinical trials drawing on PARIHS [29,56,57], and (3) demonstrated strong associations between organizational context and specific staff and LTC resident outcomes and between organizational context and implementation success [26-28,37,58].

Study Purpose, Goals, and Aims

The purpose of this study is to contribute to knowledge translation science by better understanding the roles of organizational context and facilitation in implementation and improvement success. We have 2 broad goals: (1) to advance knowledge translation science by further developing and testing the PARIHS framework for research implementation and (2) to lay foundations to advance research by optimizing implementation success via effective tailoring of modifiable elements of organizational context and facilitation. Our specific study aims are to as follows: (1) to identify how context influences success of implementation and of quality improvement initiatives, (2) to identify and map context conditions in which facilitation affects outcomes for staff quality of work life, and (3) to identify and map context conditions in which facilitation affects resident outcomes.

We propose that improvements in care and better implementation success can be achieved by modifying elements of context, particularly inner context (immediate local setting and the organization), and through both optimal use of facilitation roles and enabling of facilitation processes [41,48,59].

Methods

Ethics Approval

Ethics approval for this study was obtained from the institutional review board of the University of Alberta (Pro00096541).

Study Design

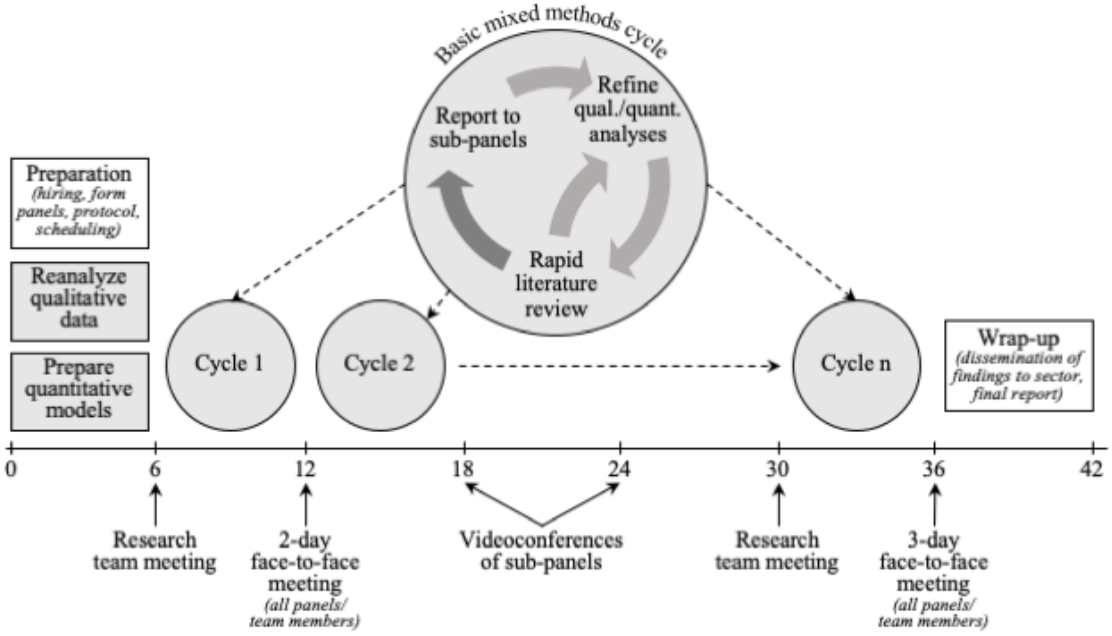
In these secondary analyses, we will apply convergent mixed methods and sequential mixed methods designs [60] to concurrently address all three of our aims.

Overall Approach

The research team includes a multidisciplinary group of researchers, 4 panels of key stakeholders who are end users, and a fifth panel of external scientific experts: (1) system-level decision- and policy makers, (2) LTC home managers, (3) direct care staff working in LTC homes, (4) people living with dementia and their family members (citizen engagement), and (5) scientists with substantive knowledge of organizational context and learning, the PARIHS framework, context, facilitation, leadership, and implementation science.

We will analyze TREC's comprehensive data holdings (qualitative and quantitative data) in an iterative process (action cycles; see Figure 1): (1) comprehensive analysis of qualitative data to derive hypotheses on links between context factors and specific outcomes not yet explored, (2) analysis of quantitative data to test derived hypotheses, and (3) mixed methods action cycles to integrate qualitative and quantitative findings. Each action cycle will consist of data analysis, rapid literature reviews, and expert panel consultations and synthesis to further refine and integrate qualitative and quantitative analyses (Figure 1).

Figure 1. Project overview.



Setting, Sample, and Data Holdings

Setting and Sample

The TREC program is situated in residential LTC in the 4 western Canadian provinces (British Columbia, Alberta, Saskatchewan, and Manitoba) where we maintain a cohort of 94 participating LTC homes. The cohort sample is a stratified (health region, owner-operator model, and bed size) random sample [61] of urban LTC homes in 5 health regions of participating provinces.

TREC Data Holdings

We have longitudinal data (Table 1) from 2 main sources: (1) TREC surveys (collected in 5 waves since 2007) of LTC homes, care units, and all levels of staff (regulated and unregulated nursing staff, allied health providers, specialists and educators, and managers) and (2) administrative data collected using the Resident Assessment Instrument – Minimum Dataset (RAI-MDS) 2.0 [62]. The RAI-MDS 2.0 is a routinely collected (quarterly, annually) and standard mandated assessment of clinical and functional outcomes for LTC residents [62]. Beyond these observational data from our ongoing cohort study, we have data from pilot studies, clinical trials, and case studies. All research data are housed in the Health Research Data Repository (University of Alberta), which provides virtual data access for team members within a highly secure environment. Data are extensively processed to exceed Canadian Institute for Health Information standards for RAI-MDS 2.0 data. Extensive quality assurance (during data collection and post data collection) is carried out with survey data, including assigning each resident to a single unit within a single LTC home [63].

Table 1. Overview of Translating Research in Elder Care (TREC) data holdings from 5 waves of data collection.

Data source	Participants, n				
	Wave 1 (June 2008 to July 2009)	Wave 2 (July 2009 to June 2010)	Wave 3 (September 2014 to May 2015)	Wave 4 (May 2017 to December 2017)	Wave 5 (September 2019 to March 2020)
TREC survey					
Long-term care home	36	36	91	94	91
Care unit	103	103	336	339	324
Care staff					
Care aides	1489	1506	4065	4158	3765
Nurses (registered nurses and licensed practical nurses)	277	308	767	927	931
Allied health professionals[a]	119	145	338	569	544
Specialists	24	21	57	80	59
Managers	55	69	168	193	199
Physicians[b]	9	16	0	0	0
Resident Assessment Instrument – Minimum Data Set 2.0					
Full assessments	5326	5087	13,956	12,290	9832
Quarterly assessments	12,195	11,453	19,467	19,240	14,238
Unique residents	5593	5549	14,139	13,852	13,158
Case studies[c]					
Interviews	70	0	0	0	0
Field notes	22	0	0	0	0

[a]Allied health professionals surveyed include rehabilitation therapists (physical therapists and occupational therapies); clinical pharmacists; respiratory therapists; recreation therapists; social workers; dieticians; speech language pathologists; rehabilitation therapist assistants, attendants, and aides; and recreation therapist assistants, attendants, and aides.

[b]Physicians were not included in waves 3-5 because relatively few are regular participants in long-term care (LTC) delivery in our Canadian LTC system.

[c]Case studies include interview data with LTC direct care staff and management and administrative staff, and field notes from nonparticipation observation and document review.

Clinical Microsystems

We are able to link TREC data from multiple sources at the level of the clinical microsystem (LTC resident care unit). Data are linked by assigning residents and staff to specific care units (clinical microsystems) to create longitudinal data sets at the care unit level within LTC homes. The clinical microsystem, a central concept in quality improvement science, is the level where care is organized and delivered [64,65] and where targeted strategies are most likely to improve quality [66-68]. An innovation in the TREC research program has been to link data at the LTC resident care unit level, including administrative data (eg, standard assessments of residents). We showed that the care unit is an appropriate level to introduce and test interventions, and that it can be characterized by core internal context constructs [26,27,29,56]. We demonstrated that measuring quality indicators at the LTC home level masks important variance between care units within LTC homes [54,69].

Measures

Survey Data

Data captured in the TREC survey include (1) structural characteristics: LTC home surveys completed by the LTC home administrator and unit surveys completed by the unit care manager and (2) individual measures from managers, regulated nursing staff, allied health staff, and unregulated care aides (nursing assistants).

Examples of structural characteristics are size and the owner-operator model of LTC homes and type and staffing level of care units. Individual surveys are a suite of instruments and questions that capture demographic characteristics, best practice use, quality of work life, and organizational context. Quality of work life variables are captured using validated measures. They include burnout (Maslach Burnout Inventory) [70], physical and mental health (Short Form-8) [71], work engagement (Utrecht work engagement scale) [72], psychological empowerment (Psychological Empowerment Scale) [73], organizational citizenship behavior [74], job satisfaction

(positively phrased version of Michigan Organizational Assessment Questionnaire Job Satisfaction Scale) [74], and responsive behaviors of residents toward staff [75].

Organizational context is captured using the Alberta Context Tool (ACT) [54,55]. We developed the ACT based on the PARIHS initial conceptualization of context, which includes culture, leadership, and evaluation (feedback of data to end users). We added constructs substantiated in health services literature [76], such as social capital, formal and informal interactions (2 communication concepts), organizational slack, and resources [55]. The ACT has measured context at the LTC home, unit, and group levels [27,28], but it is designed specifically for the clinical microsystem or resident care unit level [26-29]. It has had extensive psychometric assessments [54,55,77-79].

Resident Data

We have access to deidentified resident data from the RAI-MDS 2.0 for each of the 94 participating LTC homes. From our 5 large waves of data collection, we have over 500,000 resident data records. Further, we can link these data to external Continuing Care Reporting System data nationally (eg, Canadian Institute for Health Information [80]) and provincially (eg, Alberta Health [81]), and to other Canadian administrative databases (eg, Discharge Abstract Database [82]).

Clinical Trial Data

Table 2 provides an overview of data from our 2 completed clinical trials: Improving Nursing home care through Feedback On performance (INFORM) data [50,83,84] and Safer Care for Older Persons [in residential] Environments (SCOPE) [56,85,86]. The INFORM trial supported LTC home managers as they used our feedback from survey findings. INFORM included 143 care units from 58 LTC homes. It gathered quantitative data from surveys, reports, and workshop and rating evaluations, along with qualitative data from focus groups, interviews, and reports (process evaluation data).

The SCOPE trial examined the effects of empowering care aides to lead quality improvement strategies in their care unit. SCOPE included 408 participants from 45 LTC homes. It gathered quantitative data as rich survey data from individuals, teams, and leadership, and qualitative data from interviews, focus groups, and observation (process evaluation data).

Table 2. Overview of Improving Nursing home care through Feedback On perfoRMance and Safer Care for Older Persons [in residential] Environments trial data.

Data source	Value, n
Improving Nursing home care through Feedback On perfoRMance	
Long-term care homes	58
Care units	143
Surveys (participants)	
Fidelity checklist	278
Workshop evaluation	355
Report back slides	167
Focus groups (units)	60
Interviews (units)	11
Engagement ratings (units)	117
Safer Care for Older Persons [in residential] Environments	
Long-term care homes	45
Participants	408
Surveys (participants; completed 4 times)	
Team level	159
Individual level	478
Leadership level	210
Interviews or focus groups (participants)	331
Observational data (sessions observed)	204

Case Study Data

We have data from 3 extensive ethnographic case studies completed in TREC phase 1 (2007-2012) [87,88]. We obtained 70 interviews and 22 sets of field notes from nurses, care aides, managers, allied health personnel, and family of residents from 3 LTC homes in Alberta, Saskatchewan, and Manitoba. In-person interviews (2008-2010) were semistructured. Ethnographic observations (2008-2009) were written as field notes by research associates. The purpose of the original ethnographic case studies was to explore how organizational

context mediates staff use of evidence-based best practices in LTC homes [87].

Additional Variables Derived From TREC Data

Facilitation, implementation success, and improvement success are not directly available in our data, but we will derive the variables from our INFORM and SCOPE trial data. Many quality improvement interventions in health care settings target health care providers' adoption of evidence-based best practices [89]. Our team has used survey data on staff adoption of best practices as a proxy for implementation success [56,85,90,91]. Specifically, we measured conceptual use of best practices [90,92] and instrumental use of best practices (applying best practice knowledge) [37,92]. In this study, we will draw on our earlier work to derive variables of implementation and improvement success using INFORM and SCOPE trial data [50,57]. We will rank the sites in each of our 2 trials on the basis of success, then derive a "success" variable, and experiment to find an optimal derivation.

We have published one conceptualization of facilitation [48]. Other data derivations are possible from examining role or process. We will rank facilitation effectiveness as we rank implementation and improvement success to derive a facilitation score by site.

Analyses

Qualitative Data Analyses

We will examine qualitative data from our case studies and INFORM and SCOPE trials (process evaluation data). For the case study data, we will search for evidence on context elements that most strongly influence the association between facilitation and staff quality of work life, and between facilitation and improvements in resident outcomes. We will propose hypotheses for quantitative analysis that will contribute toward aims 2 and 3. For the trial data, we will look for evidence on the context elements that most strongly drive better trial intervention delivery, enactment, and receipt, and on improvement success of the trial. This will contribute toward our first aim of understanding implementation success. We will use ATLAS.ti software [93] to support data management and analysis and visualization of findings.

We will examine the data first with the lens of the PARIHS framework (eg, context and facilitation) and then augment with other key theoretical perspectives (eg, adaptive leadership and sense-making) [94,95]. We will use directed coding [96], guided by PARIHS concepts, and open coding [96] to capture concepts that are not part of PARIHS or that describe relevant staff and resident outcomes. Two coders will read and code each transcript and write a summary. Senior qualitative researchers on the coding team will review summaries. Codes will be added and refined, and summaries updated as needed.

Coders will then use the summaries to synthesize findings into a matrix to illustrate the concepts of interest and potential relationships among them. They will include sample quotes to exemplify the concepts. Matrices will be examined by senior team members and refinements made as needed. We will use the matrices to create network figures, using the network feature of ATLAS.ti software to depict relationships identified in the data. Networks will be reviewed by the full team and refined. Matrices and networks will be examined across cases to identify patterns and areas of contradiction. Questions from the full team will be explored by the coding team, who will look back at the original source data and examine the audit trail of the initial coding, summaries, matrices, and networks.

Quantitative Data Analyses

Our quantitative working group will analyze quantitative data from TREC surveys and RAI-MDS 2.0. We will be able to measure many constructs derived from qualitative analyses. TREC data are of high quality (few missing data and high response rates) and have been collected, cleaned, and processed through a rigorous process [97]. We will use a variety of statistical software packages for this work, such as SAS (SAS Institute), SPSS (IBM Corp), R (R Foundation for Statistical Computing), and STATA (StataCorp).

We will conduct basic descriptive and bivariate analyses, followed by more advanced statistical modeling using; for example, general estimating equations, hierarchical linear mixed models, and generalized linear mixed models. These enable us to adjust for complex nested structures of our data [26,38]. We will also explore the use of structural equation modeling and configurational modeling [98,99]. We will adjust our analyses as appropriate for different outcomes, including resident or care staff characteristics (depending on outcome), care unit characteristics, LTC home characteristics, and regional features depending on the addressed aim. We will begin with an approach that examines a standard set of context influences and assess it across staff and resident outcomes at unit and individual levels (aims 1 and 2). Based on these analyses, with the input of our qualitative team and panels, we will identify patterns and trends over time.

Mixed Methods Analysis

We will adopt convergent and sequential mixed methods models to obtain different but complementary data on the same problem for a more complete understanding [100]. In a convergent model, we will first analyze qualitative and quantitative data separately and independently, then integrate results in matrices, and interpret how the 2 sources of results converge or diverge [60,101]. In sequential modeling, results of qualitative analysis will inform the quantitative analysis and vice versa [60].

As an example, we will complement the PARIHS framework with other conceptual frameworks (eg, adaptive leadership and sense-making) [94,95,102] and form hypotheses related to our aims, including hypotheses on how context factors influence implementation outcomes. We will then test the hypotheses by analyzing both the quantitative and qualitative data and explore support or nonsupport of interrelationships. Next, we will focus on interactions among the context factors and interaction between context and facilitation based on our qualitative analyses, forming additional hypotheses. We will test these additional hypotheses with quantitative analysis. When unanticipated results emerge from the quantitative analysis, we will use qualitative analysis to explore processes and mechanisms explaining the results.

Refinement of Analyses

We will work iteratively with our stakeholder and expert panels to further inform and refine analyses. We will hold 2 virtual facilitated meetings with all panels (Figure 1). Before meetings, work groups will prepare summary reports of research findings and a focused set of guidelines and questions that are tailored to each panel. During meetings, the external expert panel will comment on summary reports and advise through scientific and theoretical lenses on early findings presented, most promising and important avenues to pursue, and areas not yet identified that our data would support for further exploration. The decision- and policy maker and LTC home manager panels will comment and advise on these same aspects through a lens of system management and utility of findings. The direct care staff panel will provide a frontline perspective on whether and how our findings could be useful to them and suggest areas we may not have considered. The citizen engagement panel will also comment and advise on whether and how our findings could be useful to them and suggest areas we may not have considered, from the perspective of findings important to their constituencies. This panel approach assists us with direction and focus, to keep our results both scientifically and practically relevant.

Results

The results of the secondary data analysis are expected by the end of 2023.

Discussion

This project responds to (1) calls to improve understanding of the mechanisms by which context and facilitation function, (2) criticisms that the aging field (like many) is rich in data but impoverished in theory, and (3) calls for optimized use of longitudinal data to advance the science of aging and appropriately inform policy makers on complex issues affecting aging populations [14,15,103,104].

We expect to advance the PARIHS framework by better describing the mechanisms by which context and facilitation influence implementation and improvement processes. We will identify specific factors of organizational context (such as slack time and space, culture, communication, and resources) and facilitation and understand how they interact and affect outcomes. We will elaborate on inner (local setting or organization) versus outer (health system, or policy or political infrastructure) context conditions.

We anticipate generating a stronger evidence base for large pragmatic implementation and quality improvement trials. An advantage of our study is the potential to generate both scientific and practical working knowledge through our integrated knowledge translation approach [105]. This maintains relevant to end users of the LTC system (residents and their family members) and the LTC care staff and managers who run the system and who are ultimately responsible for large-scale implementation of evidence-based choices.

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Data Availability

The data used for this article are housed in the secure and confidential Health Research Data Repository (HRDR) in the Faculty of Nursing at the University of Alberta, in accordance with the health privacy legislation of participating Translating Research in Elder Care (TREC) jurisdictions. These health privacy legislations and the ethics approvals covering TREC data do not allow public sharing or removal of completely disaggregated data (resident-level records) from the HRDR, even if deidentified. The data were provided under specific data sharing agreements only for approved use by TREC within the HRDR. Where necessary, access to the HRDR to review the original source data may be granted to those who meet prespecified criteria for confidential access, available at request from the TREC data unit manager, with the consent of the original data providers and the required privacy and ethical review bodies. Statistical and anonymous aggregate data, the full data set creation plan, and underlying analytic code associated with this paper are available from the authors upon request, understanding that the programs may rely on coding templates or macros that are unique to TREC.

Authors' Contributions

CE and PN conceived the study. CE designed and helped draft the final study protocol and is the principal investigator of the grant. YS helped draft the final study protocol. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Canadian Institutes of Health Research (CIHR) (Instituts de recherche en santé du Canada) - Knowledge Translation Research (Recherche sur l'application des connaissances) (Canada).
[PDF File (Adobe PDF File), 73 KB - resprot_v11i9e40611_app1.pdf]

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Abbreviations

ACT: Alberta Context Tool
HRDR: Health Research Data Repository
INFORM: Improving Nursing home care through Feedback On perfoRMance
LTC: Long-term care
PARIHS: Promoting Action on Research Implementation in Health Services
RAI-MDS: Resident Assessment Instrument – Minimum Dataset
SCOPE: Safer Care for Older Persons [in residential] Environments
TREC: Translating Research in Elder Care

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Protocol

Testing and Optimizing Guided Thinking Tasks to Promote Physical Activity: Protocol for a Randomized Factorial Trial

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Abstract

Background: Insufficient physical activity is associated with various health risks; however, most current physical activity interventions have critical barriers to scalability. Delivering interventions via technology and identifying active and inert components in early-phase development are ways to build more efficient and scalable interventions. We developed a novel intervention to promote physical activity that targets 3 brief guided thinking tasks, separately and in combination, using brief audio recordings: (1) episodic future thinking (EFT), (2) positive affective imagery (PAI), and (3) planning.

Objective: The aim of this GeT (Guided Thinking) Active study is to optimize a scalable guided thinking intervention to promote physical activity using principles of the Multiphase Optimization Strategy (MOST). Mechanism-focused analyses will inform which components are optimal candidates for inclusion in an intervention package and which need refinement.

Methods: We will enroll 192 participants randomized to receive intervention components delivered via an audio recording that they will listen to prior to weekly in-lab physical activity sessions. Participants in the high dose conditions will also be instructed to listen to the audio recording 4 additional days each week. We will evaluate effects of the components on physical activity over 6 weeks in a 2 (EFT vs recent thinking) × 2 (PAI vs neutral imagery) × 2 (planning vs no planning) × 2 (dose: 5×/week vs 1×/week) full factorial randomized trial.

Results: The National Cancer Institute funded this study (R21CA260360) on May 13, 2021. Participant recruitment began in February 2022. Data analysis will begin after the completion of data collection.

Conclusions: The GeT Active study will result in a scalable, audio-recorded intervention that will accelerate progress toward the full development of guided thinking interventions to promote physical activity.

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International Registered Report Identifier (IRRID): DERR1-10.2196/40908

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KEYWORDS

physical activity; optimization; brief intervention; episodic future thinking; positive affective imagery; planning; exercise

Introduction

Background

Insufficient levels of regular physical activity, defined as less than 150 minutes a week of moderate-to-vigorous physical activity (MVPA), are associated with numerous health risks, including cardiovascular disease, obesity, and various cancers [1-7]. Nearly 50% of adults in the United States report insufficient levels of physical activity, and 26.6% report no regular activity [8]. Objective assessments indicate that rates

of physical activity are even lower than self-reported rates [9,10]. Most current physical activity interventions require significant resources that create barriers to scalability (eg, staff time, significant participant burden) [11-15]. Most interventions are also "black boxes," in that they include multiple intervention components (eg, *M*=8.4 components among 26 interventions [16]) without knowing which specific components are active and which are inert. This also creates barriers to efficiently disseminating the intervention and refining ineffective components [15]. Therefore, there is a need for novel intervention strategies to promote regular physical activity that are both effective and scalable.

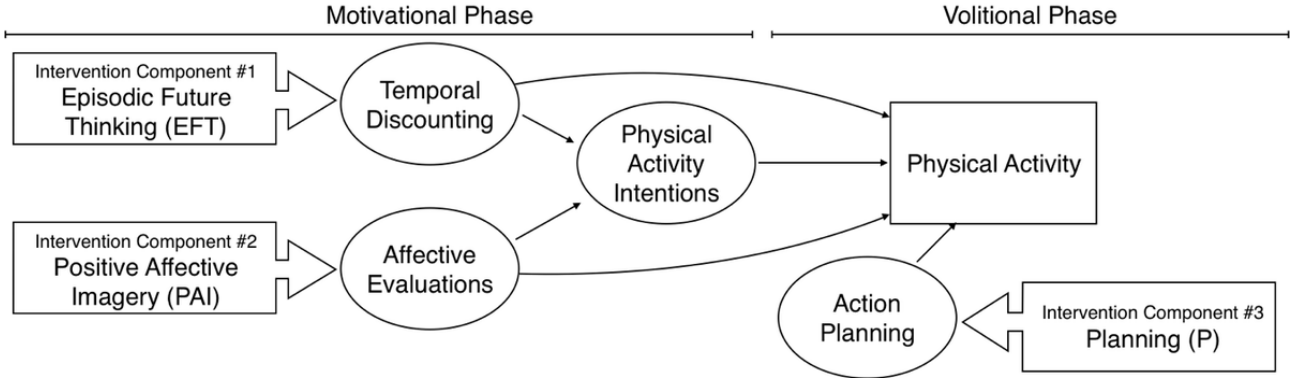
Delivering physical activity interventions via technology-based platforms can address scalability and dissemination barriers by minimizing cost and resource demands. Physical activity interventions delivered via smartphone apps, websites, and audio recordings [12,13,17] have proven to be feasible and effective [12-14,18,19]. However, effective technology-based interventions [14,18] have the same "black box" problem as other interventions. Identifying active and inert intervention components in early-phase development (versus later on in the process) is a means to build more efficient and scalable interventions and is aligned with current intervention development frameworks, such as the Multiphase Optimization Strategy (MOST) [15], Obesity-Related Behavioral Intervention Trials (ORBIT) model [20], and Science of Behavior Change [21].

We developed a novel intervention to promote physical activity that targets 3 brief intervention techniques, separately and in combination. Episodic future thinking (EFT) is a guided time-perspective task that directs individuals to actively imagine themselves in the future at a meaningful event [22-27]. Positive affective imagery (PAI) is a guided imagery task to increase positive affective associations with a target behavior and reframe related physical and physiological experiences as positive [22,26,28]. Planning is a guided task in which individuals specify when, where, and how a target behavior will be enacted [29-31].

In developing and optimizing a scalable physical activity intervention, EFT, PAI, and planning have several advantages as potential intervention components. First, each component can be delivered as a brief intervention (ie, <3-4 minutes each). Lack of time is a common barrier to physical activity [32,33]; therefore, brief intervention components are optimal. Given their brevity, these components can be used in a delivery mode (ie, guided audio recording) that is easily scaled and disseminated. Second, EFT, PAI, and planning have demonstrated positive effects on physical activity and other health behaviors [17,34-41]. EFT is a novel intervention technique for physical activity but has been shown to influence dietary behavior [22,26,28] and smoking reduction [42].

Third, each component targets a different putative mechanism and thus different barriers to activity (Figure 1). A key motivational barrier to activity is the temporal trade-off that exists between health benefits of physical activity that are temporally distal (eg, weight control, disease prevention) and costs that are immediate (eg, time, physical exertion [43-45]). EFT targets and reduces temporal discounting rates and preference for immediate versus delayed reward in smoking and dietary choices [23,42]. Experiencing physical activity as affectively unpleasant is a common barrier to regular activity [46-48]. PAI can positively influence affective evaluations of physical activity [49]. Action planning is hypothesized to result from the planning intervention component. Action planning reliably predicts physical activity [30,50-52] and addresses a critical barrier to physical activity change: intentions not reliably leading to activity [53-55]. Finally, the components target mechanisms in 2 distinct phases of physical activity change: (1) motivational and (2) volitional (Figure 1) [56,57]. Targeting components in both phases is expected to lead to greater activity because both motivational and volitional processes are needed to change behavior [56]. Therefore, we expect a combination of components to have a stronger effect than any 1 component alone.

Figure 1. Conceptual model of intervention components, putative mechanisms, and behavior change phases.



Optimization of the Novel Intervention

To optimize the intervention with EFT, PAI, and planning, the unique and combined effects of the components need to be compared as they have previously only been examined separately, and their combined effects on physical activity are unknown. Three possible effects have implications when deciding which combination of components is optimal [15]: (1) independent effects, in which one component's effect does not depend on another component; (2) synergistic effects, in which a component's effect is strengthened by the presence of another

component; and (3) antagonistic effects, in which a component effect is weakened by the presence of another component.

Comparing different frequencies of intervention use (ie, dosage) and how different doses influence the effects of EFT, PAI, and planning provides additional information for determining optimal combinations (eg, whether the effects of some components are strengthened by more frequent use). Optimal dosage of physical activity interventions is typically unexamined and a part of the "black box." Determining mechanisms of the intervention components also accelerates the optimization process. We will use an experimental medicine approach [21,58] to test the extent to which (A) each component changes its putative mechanism, and (B) each mechanism is prospectively associated with physical activity, with the aim of elucidating why the intervention components are (or are not) effective [59].

Objective of the GeT (Guided Thinking) Active Study

The overall objective of the GeT Active study is to optimize a scalable guided thinking intervention to promote physical activity, using principles of the MOST framework [15]. We will evaluate effects of the components on physical activity over 6 weeks in a 2 (EFT vs recent thinking) × 2 (PAI vs neutral imagery) × 2 (planning vs no planning) × 2 (dose: high vs low) full factorial randomized trial. We will use the following criteria to evaluate findings and identify the optimal combination of intervention components: effect of components on physical activity, efficiency (ie, identify inert components, antagonistic effects), participant burden (ie, total recording length, intervention dose), and acceptability of each guided thinking component. Mechanism-focused analyses will inform which components are optimal candidates for inclusion and which need refinement or reconsideration [59].

Methods

Intervention Component Evaluation

We plan to enroll 192 participants who will be randomized to receive the intervention components delivered via an audio recording that they will listen to prior to the weekly in-lab physical activity sessions. Participants in the high dose conditions will also be instructed to listen to the audio recording 4 additional days during each week. We will use a full factorial design whereby participants will be randomized to 1 of 16 combinations of the 4 intervention components (Table 1). The 4 intervention components are listed as follows.

The first intervention component is episodic future thinking (EFT). In the baseline session, participants will complete an interview with a research assistant (RA) to identify and imagine a positive event that is important to them and that they will experience 4-6 months into the future. In the audio recording (2 minutes and 35 seconds in length), participants will be prompted to imagine themselves at that future event in specific and vivid detail (eg, where they will be, what they are doing, how they are feeling), including imagining they have accomplished their goal of becoming more physically active over the preceding months. The content is similar to EFT tasks that have positively influenced food choice [22,28]. Participants not assigned to receive the EFT audio recording will be guided in an episodic recent thinking (ERT) interview and audio-recorded task (2 minutes and 45 seconds in length) to think in similar detail about a regular habit they enjoy and engaged in during the past week.

The second intervention component is positive affective imagery (PAI). Participants will be guided by the audio recording (3 minutes and 50 seconds in length) to think about positive feelings and associations with physical activity in specific, personal, and positive detail. They will imagine themselves engaging in physical activity, reframing physical sensations with positive attributions, and feeling satisfied about the challenge and accomplishment of physical activity. The content is similar to PAI tasks in previous studies [17,28,34]. Participants not assigned to PAI will receive a neutral imagery recording (2 minutes and 20 seconds in length) and will be guided to imagine specific physical sensations (ie, movements, muscles used) of a routine, daily (nonphysical) activity.

The third intervention component is planning. Participants will be guided by the audio recording (2 minutes and 35 seconds in length) to think about the remainder of their week and when (ie, days, times), where (ie, walking path, gym), and how (ie, walking with friend, alone) they plan to attain their remaining MVPA to reach the weekly 150-minute goal. The content is similar to planning tasks that have been shown to influence physical activity [38,40,41]. Participants not assigned to receive the planning component will not receive a control recording (ie, planning vs no planning).

The fourth component is the intervention dose. Participants will receive their assigned combination of intervention components either once a week during the in-person visit (low dose) or 5 times a week (in-person visit plus 4 additional days; high dose). Participants in the high dose conditions will receive instructions on how to access their audio recording file and will be assigned 4 additional days, including 1 weekend day, to listen to their audio recording. They will receive text message reminders to listen to the recording on those 4 days.

Table 1. Experimental condition assignments in the full factorial design.

	Experimental condition assignments															
Component	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
EFT[a]	Y[b]	Y	Y	Y	N[c]	N	N	N	Y	Y	Y	Y	N	N	N	N
PAI[d]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N
Planning	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N
Dose	Hi[e]	Lo[f]	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo

[a]EFT: episodic future thinking.

[b]Y: yes.

[c]N: no.

[d]PAI: positive affective imagery.

[e]Hi: high.

[f]Lo: low.

In each audio recording, the guided thinking components always appear in the following order: EFT/ERT, PAI/neutral imagery, and planning. We selected this order to minimize the cognitive load that temporal switching between tasks will require. This order allows listeners to imagine a future (or past) event first and then switch to the guided thinking tasks that are more present-focused. Planning is the final guided thinking component because it is designed to leverage the increased motivation for physical activity targeted by the other components and focus on enacting physical activity (ie, volitional phase). Table 2 includes examples of key pieces from each of the audio recording scripts.

Table 2. Examples of key pieces from each of the audio recording scripts.

Audio recording	Examples of key script pieces
EFT[a]	• "Think back to the specific, positive event that you identified during your initial visit. You are looking forward to this event that will happen several months from now." • "Now, imagine that you are at this event, and you have accomplished your goal of becoming more physically active." • "Imagine the details of the event as specifically and vividly as you can…"
ERT[b]	• "Think about the routine activity that you identified during your initial visit. This is a routine activity or habit that you do every week." • "Imagine the details as specifically and vividly as you can, as if it were happening again right now…"
PAI[c]	• "Select an aerobic physical activity, such as brisk walking or hiking. Imagine yourself doing this activity today." • "Think about the positive benefits of this activity for you…how it might enable you to do more than you could before, and make your daily life feel more enjoyable…" • "Imagine yourself doing this activity as vividly as you can…your body might feel warm…you might feel fatigued…the increase in sensations can be a good thing…your body is responding to the challenge you are giving it and becoming stronger, healthier, energized…" • "Imagine that you've finished your activity today and you feel satisfied, confident, and energized…"
Neutral imagery	• "Imagine you are doing a simple task or activity, an activity that you may do every day and that does not require much effort, such as folding laundry, household shopping, getting dressed for the day, or making your bed…" • "Imagine yourself completing this activity from start to finish as vividly as you can…imagine your body moving and using your body to complete the task." • "What muscles are you using to complete this task? Do you feel your muscles contracting?"
Planning	• "Think about where you are currently in your week and how many minutes of activity you still need to attain your goal of two and a half hours…" • "What days of the week can you most easily schedule physical activity? What time during these days can you realistically engage in activity?...Where will you do the activity?...How will you do it? Will you be alone or with a friend?"

[a]EFT: episodic future thinking.

[b]ERT: episodic recent thinking.

[c]PAI: positive affective imagery.

Study Design

We will use a 2 (EFT vs recent thinking) × 2 (PAI vs neutral imagery) × 2 (planning vs no planning) × 2 (dose: high vs low) full factorial design with a 1:1 allocation ratio to evaluate the components and their combinations in this randomized trial. This is not a 16-arm trial requiring comparison on individual experimental conditions; instead, the design allows for comparisons of means computed across aggregates of experimental conditions (ie, each comparison will involve all 16 experimental conditions). For example, the main effect of the EFT component will be tested by comparing the mean MVPA for the half of the sample who receive the EFT component (ie, those in conditions 1, 2, 3, 4, 9, 10, 11, and 12 in Table 1) to the mean MVPA for the half of the sample who do not receive EFT (ie, those in conditions 5, 6, 7, 8, 13, 14, 15, and 16 in Table 1).

Ethics Approval

The study was approved by the Southern Methodist University Institutional Review Board (H21-003-BALA) on January 14, 2021.

Eligibility

The inclusion criteria are that participants must (1) be 18-64 years of age, (2) be capable of providing informed consent, (3) have access to a smartphone, (4) be willing to attend all study visits and comply with the protocol, (5) be conversant in English, and (6) not currently meet recommended physical activity guidelines (defined as <150 minutes/week of self-reported MVPA). For safety considerations that could make moderate-intensity activity unsafe [60], we will exclude participants who report any of the following conditions: coronary artery disease, stroke, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, diabetes, BMI>40, or orthopedic problems that limit physical activity.

Recruitment

We will recruit 192 community-dwelling adults who are not currently meeting recommended physical activity guidelines. Recruitment strategies will focus on online postings and social media advertisements on various platforms (eg, Facebook, Instagram, NextDoor, Craigslist) in the Dallas-Fort Worth area. We will also actively recruit adults from traditionally underrepresented groups through advertising and postings in online outlets and community facilities that serve racial and ethnic minority groups.

Screening

Initial eligibility will be determined with an online prescreen questionnaire, in which potential participants will report their physical activity for a typical week over the past 6 months using items from the International Physical Activity Questionnaire (IPAQ) [61]. They will also report on the inclusion criteria and exclusionary health conditions. Eligible participants will be contacted to schedule a telephone screen and a baseline study visit and to complete an initial COVID-19 screen in which they will be asked to self-report COVID-19 symptoms and their vaccination status.

On the day prior to the baseline study visit, we will assess participants' physical activity during the past week using the telephone-based 7-day Physical Activity Recall (PAR), a valid and reliable measure of physical activity [62]. Participants who report >150 minutes of MVPA on this assessment will be excluded from participation. We will conduct this assessment on the day prior to the baseline visit to avoid turning away ineligible participants after they have already shown up in person. This assessment will serve as the baseline measure of participants' physical activity.

Randomization

We will stratify randomization based on 2 levels of baseline MVPA to explore the extent to which baseline MVPA moderates intervention effects: (1) individuals who report <60 minutes of weekly MVPA (ie, inactive or underactive) and (2) those who report between 60 and 149 minutes of weekly MVPA (ie, insufficiently active). These MVPA cutoffs reflect meaningful distinctions in current physical activity recommendations [1]. We will aim to recruit and enroll an equal number of individuals from both groups. Within each MVPA group, we will use block randomization with block sizes of 16 (ie, the total number of experimental conditions). We will use a random number generator to determine the random sequence within each block. The principal investigator will generate the random allocation sequence for each stratified randomization grouping. An RA will enroll and assign participants to their study condition.

In-person Visits

There will be a total of 7 in-person visits over the 6-week study period. During these visits, participants will listen to their assigned audio recording, engage in a supervised 30-minute moderate-intensity walk on a treadmill, and complete study measures.

Baseline Visit

After completing the informed consent process, all participants will receive the same physical activity prescription (ie, >150 MVPA minutes/week) that is consistent with current recommendations [1]. A trained RA will provide instructions about increasing regular physical activity (eg, weekly recommendations, modes of activity) to attain 150 MVPA minutes/week. Participants will be instructed to focus on brisk walking to reduce potential variability in responses to different modes of physical activity and because walking is the preferred mode of activity among the general population [63]. All participants will be instructed to exercise at a moderate intensity.

Prior to listening to their assigned audio recording, participants will complete a baseline measure of study variables and demographics. Participants will then listen to their assigned audio recording before completing the in-lab brisk walking session. The audio file will be stored on a secured website and accessed via a tablet. Participants will be instructed to sit comfortably, close their eyes, and pay close attention to the guided thinking tasks. After listening to the audio recording and before walking, participants will complete assessments of the putative mechanisms.

Participants will receive instructions on how to wear a hip-worn accelerometer (ActiGraph wGT3X-BT) and then complete a supervised 30-minute brisk walk on a treadmill. Participants will also wear a heart rate monitor to ensure their walking intensity remains in the moderate range (ie, 64%-76% of their estimated maximal heart rate calculated using the formula: 220 − age). We will instruct participants to use the walking intensity to guide their unsupervised walking sessions during the remainder of the week. Participants will complete assessments of affective response, perceived exertion, and arousal during and immediately postexercise. Following the brisk walking session, participants will be reminded to aim for an additional 120 minutes (2 hours) of activity during the upcoming week, wear the accelerometer every day, listen to the audio recording on the designated days (high dose conditions).

Weekly Visits

During the weekly visit, the previous week's data from the accelerometer will be downloaded and recorded. The RA will then conduct a 7-day PAR with participants to assess self-reported physical activity over the previous week. Participants in the high dose conditions will be asked to report their adherence to listening to the audio recording. The remainder of the weekly visits will follow the same procedure as the baseline visit. In the visits at weeks 3 and 6, participants will also complete a questionnaire that includes several exploratory variables assessed in the baseline questionnaire.

Study Outcomes

Primary Outcome: Physical Activity

The primary outcome will be weekly MVPA minutes assessed via hip-worn accelerometers (ActiGraph wGT3X-BT). Participants will wear the accelerometers for 1-week periods throughout the 6-week intervention. Participants will be asked to wear the device every day during waking hours, removing it only for sleep or when engaging in activities involving water (eg, showering, swimming). Data from accelerometers are well-validated [64,65]. We will use self-reported MVPA minutes using the 7-day PAR as a secondary measure of physical activity.

Mechanisms

Affective Evaluations

We will use measures of affective response to exercise and intrinsic motivation for exercise to assess affective evaluations. The Feeling Scale (FS) [66] measures affective response to exercise and will be assessed during and postexercise for the in-person walking sessions each week. The FS is a single-item measure of core affect, in which participants rate their current feelings on an 11-point scale ranging from −5 (very bad) to 5 (very good). The intrinsic subscale of the Behavioral Regulations in Exercise Questionnaire (BREQ-2) [67] will be administered after listening to the audio recording in person. Intrinsic motivation is assessed with 4 items (eg, "I exercise because it's fun") on a 5-point response scale ranging from 0 (not true for me) to 4 (very true for me).

Temporal Discounting

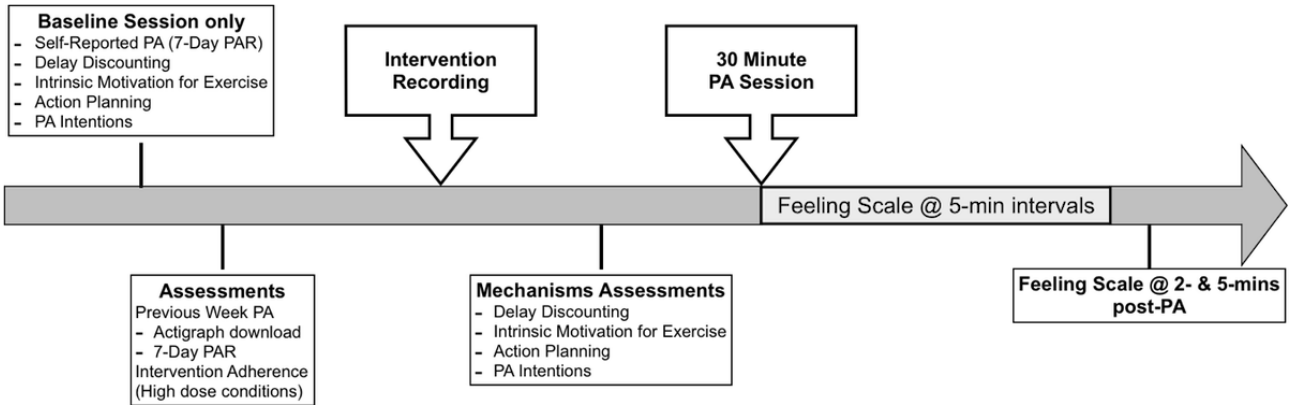
We will use a computerized delayed discounting task [68] to assess preference for immediate versus future rewards. This task will involve participants indicating their preference for smaller quantities of money that are available immediately versus larger amounts of money available sometime in the future.

Action Planning

A 4-item measure of action planning [30] will be administered after participants listen to the audio recording in person each week. Items (eg, "I have made a detailed plan regarding when to exercise") are rated on a 4-point response scale ranging from 0 (completely disagree) to 3 (completely agree).

Figure 2 shows the assessment schedule of the key study variables.

Figure 2. Timing of assessments, intervention delivery, and physical activity within each in-person session. PA: physical activity; PAR: Physical Activity Recall.



Intervention Adherence

All participants will listen to their assigned intervention recording during the in-person visits. For participants in the high dose condition, we will assess adherence via 2 sources: self-reports and tracking data that indicates access and time spent on the audio recording. For self-reported adherence, high dose participants will be asked at the beginning of each in-person visit to indicate how many days during the past week they listened to the audio recording.

Optimization Decisions

Following recommendations for optimization [15], we will start by examining main effects of the 4 intervention components, provisionally include components that have a significant effect on physical activity, and provisionally exclude components that do not. Next, we will examine interactions, starting with the 2-way interactions, to determine whether any decisions about provisional inclusion and exclusion should change. We will then use participant burden and acceptability to evaluate remaining potential combinations. A combination of components that results in less time for participants will be considered preferable to a longer intervention that produces the same effect on physical activity. Only guided thinking components rated as acceptable will be included in the final intervention package.

Statistical Analyses

Preliminary Analyses and Missing Data

Univariate and multivariate outliers will be identified and corrected following the data screening guidelines of Tabachnick and Fidell [69]. Patterns of missing data will be examined [70]. Multilevel modeling (MLM), which uses maximum likelihood procedures to handle missing data, will be used to address the research questions [71].

Analysis Plan

The first aim is to identify the optimal combination of components for meeting weekly physical activity minute guidelines. MLMs will be used to account for the nested structure of the data (ie, 6 weekly assessments nested within participants). Weekly physical activity minutes will be the dependent variable; time (weeks 0-5) will be a within-person predictor, and the main effects for each intervention component, along with all 2-way and higher order interactions, will be included as between-person predictors.

The second aim is to determine the mechanisms of each intervention component. A series of MLMs, similar to models of the first aim, will test the extent to which (A) each intervention component is associated with within-person change in its putative mechanism, and (B) the within-person change in each mechanism is prospectively associated with physical activity minutes.

Sample Size and Power

Based on a small-to-moderate effect size (Cohen d=0.40) [72] and assuming a correlation of at least r=.40 between pre- and postintervention physical activity levels, a sample size of 176 will be sufficient to detect significant effects with 80% power and a Type I error rate of .05. This sample size estimate was generated using the Factorial Power Plan macro in SAS software, which is specifically designed to calculate power for factorial designs [73]. The sample size (N=176) will provide a sufficient number of participants while also maintaining balanced cell sizes (n) across the 16 experimental conditions, an important design feature for maintaining power for tests of the main effects and interactions [15,74]. We will enroll a total of 192 participants to account for attrition (~10%) and to maintain balanced numbers across the conditions. The factorial design is sufficiently powered for all tests, including the interactions, because the tests involve comparisons of means computed across aggregates of experimental conditions [15,73].

Results

This project was funded by the National Cancer Institute (R21CA260360) on May 13, 2021, with a start date of May 15, 2021, and an end date of April 30, 2023. Recruitment and data collection began in February 2022, and 41 participants have enrolled in the study as of July 2022. Data collection is expected to be completed in summer 2023. Data analysis will begin after the completion of data collection.

Discussion

Study Implications

Delivering interventions to promote physical activity via technology-based platforms (eg, smartphone apps, websites, audio recordings) is a promising avenue to address scalability and dissemination barriers among existing interventions. The GeT Active optimization study is innovative because it identifies optimal combinations of intervention components and unpacks the “black box” in early-phase development (vs later on in the process), consistent with current frameworks of intervention development [15,20,21].

The results expected from the GeT Active optimization study will inform future refinements, testing, and use of these guided thinking tasks to promote physical activity. For example, if multiple combinations are equally effective for physical activity, this could result in a package of components that is flexible and customizable for future use (ie, individuals choose which components they want to use). Evidence on the effect of frequency of use (ie, dose) will be important in refining the intervention and subsequent dissemination, particularly if 1 component benefits from multiple uses but the others do not. We also anticipate a diverse sample with different baseline physical activity levels that will allow us to explore individual differences in the effect of the intervention components (eg, by race/ethnicity and physical activity levels).

The results from the GeT Active optimization study will also accelerate the development of the intervention more efficiently than standard approaches, which tend to either test multiple intervention components as an entire package or disparately in stand-alone studies [15]. By testing combinations of the guided thinking tasks and their frequency of use in a factorial study, we will know how the components work synergistically (or antagonistically) with each other rather than just their independent effects, as previous studies have done [17,23,26,35,41]. Moreover, by testing putative mechanisms of the components, we will be positioned to understand why components are (or are not) effective, which will help us identify which components need refinement, further optimization, or reconsideration [59].

Limitations

The study has a few limitations. First, the intervention lasts for 6 weeks, which is a short period of time to observe effects on physical activity. We sought to balance the need to enroll a

sufficient number of participants to provide a rigorous test of the guided thinking components and their combinations with a follow-up period long enough to observe sufficient variability in physical activity adherence. We are confident that 6 weeks will be long enough to provide meaningful tests of the components on physical activity, as prior studies have observed that participants begin to show meaningful variability in physical activity adherence within 4 to 6 weeks [75-77]. A longer intervention period is better suited for an efficacy trial in the final phase of intervention optimization (ie, evaluation) [15]. Second, participants in the high dose conditions receive reminders to listen to their audio recording 4 times per week via text message. These reminders could serve as an additional intervention component. Therefore, we opted to contact all participants 4 times per week via text message to increase study engagement for all participants and to ensure any potential effect of the reminders is constant across conditions. Third, the intervention dose amounts are at 2 extremes, once a week and 5 times per week. This will limit our ability to determine optimal intervention dosage. We will be able to clearly determine whether listening to the audio recording once a week is as effective as multiple times per week. If results indicate that listening multiple times per week is more effective, this will signal the importance of further specifying optimal doses in follow-up investigations.

Conclusion

The GeT Active study will result in a scalable, audio-recorded intervention to promote physical activity that will be ready for the next stage of optimization focused on refinement and evaluation [15]. The results will accelerate progress toward the full development of a guided thinking intervention to promote physical activity.

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Data Availability

The data generated during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

ASB, SL, and LEM conceptualized and designed the study. ASB wrote the initial draft of the manuscript. ASB, CLL, BAG, ADM, CDK, SL, and LEM made substantial contributions to the planning and design of the study and contributed to the revising and editing the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
National Institutes of Health (NIH) peer reviews.
[PDF File (Adobe PDF File), 135 KB - resprot_v11i9e40908_app1.pdf]

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Abbreviations

BREQ-2: Behavioral Regulations in Exercise Questionnaire-2
EFT: episodic future thinking
FS: Feeling Scale
GeT: guided thinking
IPAQ: International Physical Activity Questionnaire

MLM: multilevel modeling
MOST: Multiphase Optimization Strategy
MVPA: moderate-to-vigorous physical activity
ORBIT: Obesity-Related Behavioral Intervention Trials
PAI: positive affective imagery
PAR: Physical Activity Recall
RA: research assistant

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Protocol

The Early Detection and Case Management of Skin Diseases With an mHealth App (eSkinHealth): Protocol for a Mixed Methods Pilot Study in Côte d'Ivoire

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Abstract

Background: There is a high prevalence of skin diseases sub-Saharan Africa, including skin neglected tropical diseases (NTDs) that could lead to lifelong disabilities and deformities if not diagnosed and treated early. To achieve early detection and early treatment of these skin diseases, we developed a mobile health app, eSkinHealth.

Objective: This paper outlines a protocol for evaluating the effect of our eSkinHealth app in the early detection and effective management of skin diseases in Côte d'Ivoire.

Methods: A mixed methods pilot trial will be conducted in Côte d'Ivoire and will consist of 3 phases: (1) the development and improvement of the eSkinHealth app, (2) a pilot trial to evaluate the usability of the eSkinHealth app for local medical staff in Côte d'Ivoire, and (3) a pilot trial to evaluate the effectiveness of early detection and case management of targeted skin NTDs (Buruli ulcer, leprosy, yaws, and lymphatic filariasis) with the eSkinHealth app in Côte d'Ivoire. The pilot study will be implemented as a 2-arm trial with local health care providers and patients with skin NTDs over a 3-month follow-up period. The local health care providers will be assigned to an intervention group receiving the eSkinHealth app to be used in their daily practices or a control group. Training will be provided on the use and implementation of the app and the diagnostic pipeline to the intervention group only, while both groups will receive training on skin diseases. Our primary outcome is to evaluate the early detection and effective management of skin diseases using the eSkinHealth app in Côte d'Ivoire by the number of cases diagnosed and managed. Additionally, we will evaluate the eSkinHealth app with validated questionnaires and in-depth interviews. Procedures of our methods have been reviewed and approved by the Institutional Review Board of the Ministry of Health, Côte d'Ivoire and by Tulane University in 2021.

Results: This study was funded in 2021. We started the enrollment of patients in February 2022, and data collection is currently underway. We expect the first results to be submitted for publication in 2023.

Conclusions: Our eSkinHealth app is a field-adapted platform that could provide both direct diagnostic and management assistance to health workers in remote settings. The study will provide evidence for the usability and the effectiveness of the eSkinHealth app to improve the early detection and case management of skin NTDs in Côte d'Ivoire and, furthermore, is expected to contribute to knowledge on mobile health approaches in the control of skin NTDs.

Trial Registration: ClinicalTrials.gov NCT05300399; https://clinicaltrials.gov/ct2/show/study/NCT05300399

International Registered Report Identifier (IRRID): DERR1-10.2196/39867

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KEYWORDS

skin diseases; neglected diseases; skin NTDs; teledermatology; telemedicine; remote consultation

Introduction

The prevalence of skin diseases is high in sub-Saharan Africa, particularly in children, and the reported prevalence ranges from 23.3% to as high as 80.4% in this age group [1-7]. These diseases are most often overlooked due to a lack of local specialists and lack of experience among Western specialists looking at darker skin [8]. However, if left untreated, even some of the most common skin diseases could have severe complications (eg, scabies could lead to rheumatic fever and nephropathy, as well as often debilitating physical, social, and mental effects that may deprive one of educational and social opportunities [9,10]). Furthermore, some diseases, including leprosy, Buruli ulcer, lymphatic filariasis, and other skin infections, lead to lifelong disabilities and deformities if not diagnosed and treated early [9,11]. These skin infections that prevail in low- and middle-income countries (LMICs) are members of the skin neglected tropical diseases (NTDs) listed by the World Health Organization and targeted for disease control globally.

Observation of the skin could be very informative. Without undergoing invasive examinations requiring special skills and equipment, many skin diseases could be diagnosed with just sufficient patient history and observation of the skin. This is well suited to field settings in LMICs. Photos of the skin lesions could serve as an alternative to direct observation and, if of sufficiently good quality, could allow for the diagnosis to be made on-site or remotely. Telemedicine for dermatology, or teledermatology, is currently an emerging field taking advantage of this unique feature of skin diseases. A few attempts of teledermatology have been made in sub-Saharan African countries and have shown promising results [12-14]. These previous efforts have faced a number of challenges that we plan to overcome with the proposed work with the following features:

- A field-adapted mobile health (mHealth) app that could provide direct diagnostic and management assistance to health care workers in a remote setting: There is no novel tool to support teledermatology, especially in LMICs where internet accessibility and connection quality is a challenge. It is also of note that photos alone are often not adequate to make a correct diagnosis as outlined previously by Resneck et al [15]. Although clinical photos offer essential information, they need to be accompanied by some clinical information to make a more accurate diagnosis. Furthermore, such a tool needs to be optimized for use in the skin of people of color, given that diagnosis of several skin conditions on skin type IV and darker remains a challenge [16].
- A platform for storage of longitudinal patient records for improved follow-up: We have been conducting active surveillance for skin diseases in Cote d'Ivoire [1]. After providing a diagnosis, follow-up should be performed with the patient, especially as most of the skin diseases are chronic in nature; this is an ethical obligation in medicine. However, there is a lack of skills and expertise in dermatology to pursue this, which is a universal situation in most LMICs [17]. Our field is no exception, and it has been challenging to follow-up with our patients without making repeated field visits, which are often a long distance from city centers [18]. In addition, this lack of capability to follow up with patients is partly due to the lack of a system to document patient records. A platform that stores serial photo documentation of the clinical course could guide health care practitioners, both on-site and remotely, to provide better care.
- A platform for formal collection and automatic organization of clinical and image data of the skin: Currently, teledermatology is mostly done in platforms without any formal framework for the collection or organization of data [19], and there is a need for developing such a platform both for direct patient care and epidemiologic purposes, especially for the organization of clinical photos, which is a cumbersome task if done manually. Patient information management is another challenge in developing a successful teledermatology system, ensuring that patient privacy is fully protected. Nowadays, social networking sites such as WhatsApp and Facebook are sometimes used for teledermatology [20,21], but these informal platforms need to be used with care considering patient privacy. If there is a platform that addresses these gaps, this could further support data analysis and quality control.

In summary, with targeted training, a technology-assisted decision support system, and a telemedicine network, local health care workers could be leveraged to enhance the diagnosis and management of these conditions as well as support health care managers in quality control. If an mHealth app that overcomes these current gaps and weaknesses is developed, this could serve as a breakthrough to managing skin diseases in LMICs.

This project is built upon a previous project for the development of a prototype smartphone/tablet app for skin diseases, which

we named eSkinHealth. This app is aimed at on-site and remote diagnosis, monitoring, clinical decision support, and geographic mapping of skin diseases, including skin NTDs adapted for use in LMICs and for skin type IV and darker. Through this project, we will develop a powerful and comprehensive but easy-to-use mHealth app that could be used for the diagnosis and management of all types of skin conditions, especially focused for use in LMICs and for skin type IV and darker.

Methods

Study Design

A mixed methods pilot trial will be conducted in Côte d'Ivoire where there is coendemicity with multiple skin NTDs, including Buruli ulcer, leprosy, yaws, scabies, and lymphatic filariasis. The trial will consist of 3 phases: (1) development and improvement of the eSkinHealth app and the platform, (2) pilot trial to evaluate the usability of the eSkinHealth app, and (3) pilot trial to evaluate the effectiveness of early detection and case management of skin diseases with the eSkinHealth app. Phases 2 and 3 of the study will be implemented as a 2-arm trial over a 3-month follow-up.

Participant Inclusion/Exclusion Criteria

Eligible patients will be defined as those who are clinically suspected of or diagnosed with skin NTDs (Buruli ulcer, leprosy, yaws, scabies, and lymphatic filariasis) or suspected of other clinically diagnosed skin conditions, with fewer than three concomitantly identified skin conditions, and able to consent for themselves. Ineligible patients have more than three skin conditions and reside outside of the target site.

Local health care providers (ie, doctors, nurses, or community health workers/volunteers) must meet all eligibility requirements to enroll in the study. Eligible local health care providers are 18 years or older, working at primary health centers or clinics (PHCs) or within the catchment area of the selected PHCs in Côte d'Ivoire, able to read and speak fluent French, willing to participate in the pilot study for the 3-month study duration and use a provided tablet with the eSkinHealth app if they were assigned in the intervention group, and able to consent for oneself. Ineligible local health care providers will be defined as those who are planning to leave the job at the PHCs within the study period and have difficulty operating mobile devices.

Recruitment Procedure

We will select 10 to 12 PHCs in health districts with multiple skin NTDs coendemicity as our study site and allocate them equally into intervention and control arms. Targeted patients will include individuals with skin diseases identified through skin surveillance activities and who access the selected PHCs for diagnosis and treatment of their conditions. Local health care providers will be recruited purposively from our study site. A total of 44 local health care providers, including nurses and community health workers, will be selected to participate in the study; the number per PHC will be based on the population of the catchment area of the PHC. All participants will be enrolled formally only after signing the informed consent form.

Intervention

Phase 1: Development and Improvement of the eSkinHealth App and the Platform

The current prototype of the eSkinHealth app is made up of six primary functions, which include (1) patient ID and demographics, (2) symptom list, (3) symptom basic information, (4) history list, (5) record of the day, and (6) photo list (Figure 1). The content of these screens has been developed based on our previous field surveys [1] and from the research team's experience in managing dermatological patients. We have built-in some special features within each screen (Figure 2). The screen with the patient ID and demographics allows for entry of basic information, automatic calculation of BMI, and assessment of the patients' nutritional status. The nutritional status could be an important risk factor/indicator for several skin conditions, including wound healing. Patients may present with multiple skin conditions, and this could be organized and managed under the screen of the symptom list. In the screen with the symptom basic information, important information on diagnosing a skin disease is provided as a drop-down choice, so it is not missed and easy to enter. If patients are to return to the clinic, the evolution of their symptom could be seen at a glance in the screen with the history list, allowing comparison with previous symptoms. Lastly, physical examination results of a 1-day visit could be entered in the screen with the record of the day, and clinical photos could be taken, which will be automatically organized in the screen with the photo list. A unique function that we included in our tool is the itchiness and pain visual scale whereby patients themselves could touch the screen and indicate how they are experiencing these sensations each time.

This app is not a disease-specific tool and is fit for use for a wide range of skin conditions with two algorithms: one for nonulcerative skin diseases and another for wounds, a very common manifestation of the skin in LMICs but with different follow-up approaches as compared to other skin conditions. Other special features of the app include patient information security using QR codes. Patients are issued a QR code at their first visit. When they present it to a local health care provider with a device running the eSkinHealth app during follow-up visits, it allows access to their records, making their health records secure and portable.

We will conduct a series of opinion hearings, including expert panel reviews, weekly team meetings, and in-depth interviews and focus group discussions with target end users. In addition, we will develop a web-based platform to manage the case and to have a consultation with a remote health care provider. The app will sync with the platform and will include the following additional functionalities: data overview, search function, and graphical display of data.

Figure 1. Algorithm in the eSkinHealth app.

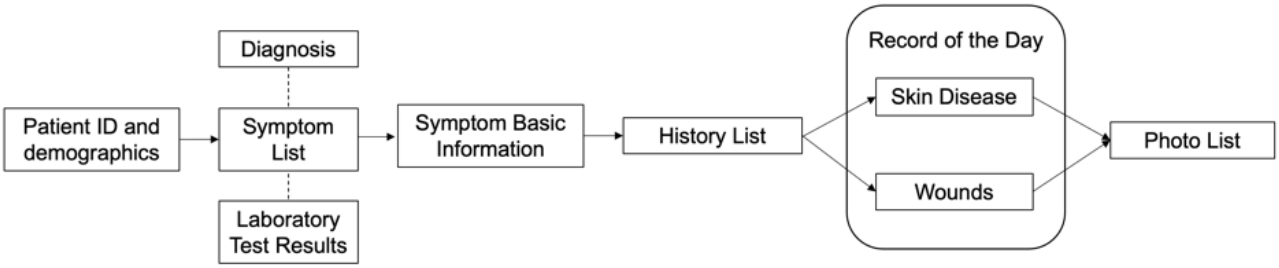
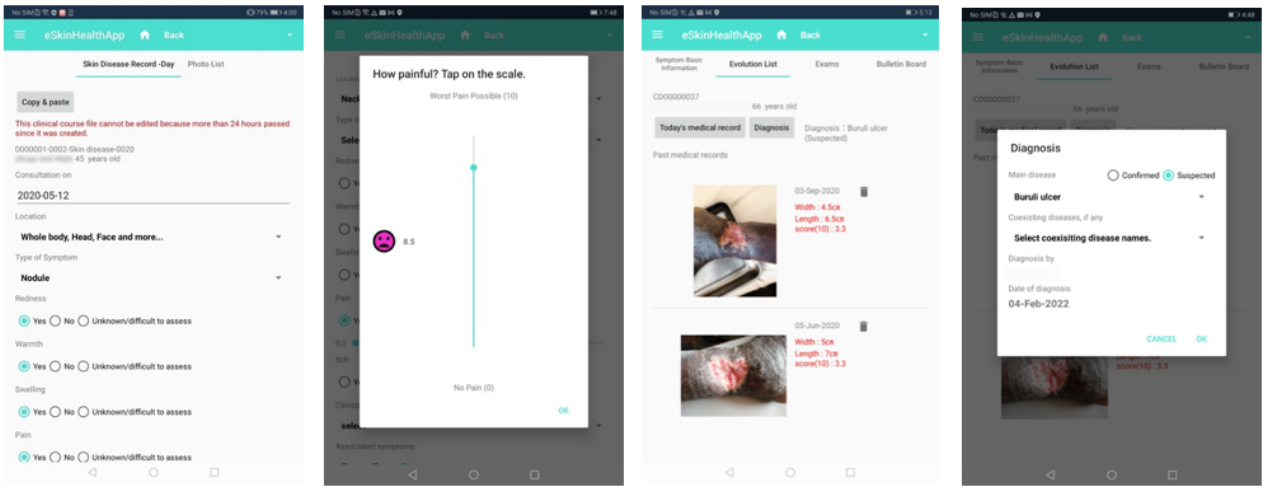


Figure 2. Sample screens of the eSkinHealth app.



Phase 2: Pilot Trial to Evaluate the Usability of eSkinHealth

We will conduct a 3-month pilot trial to evaluate the usability of eSkinHealth. Local health care providers in the intervention arm will be provided with a tablet with eSkinHealth installed and a Wi-Fi router, and will be trained on how to use the app by study staff. All local health care providers, irrespective of intervention or control arm, will be provided with a training on the screening and management of important skin diseases. We will then apply a questionnaire survey to investigate the usability of the eSkinHealth app [22]. As for usability, the questionnaire surveys will use the System Usability Scale (SUS) developed and validated by Brooke [23,24]. We will conduct the SUS over a 3-month follow-up with repeated assessments at baseline, the midpoint (6 weeks), and the end of the study (12 weeks). Furthermore, we will conduct several in-depth interviews with:

- Users (ie, local health care providers) to gather feedback on their experience, perceived value, and willingness to use the eSkinHealth app, and identify the obstacles and challenges faced in the implementation of the mobile apps
- Patients (parents or caregivers for children) to assess their willingness to have eSkinHealth used during their consultation (or consultation of their children)
- District officers and program managers to collect and further examine their opinions about the feasibility and advantages and disadvantages of adopting the eSkinHealth app by local health care providers already involved in the delivery of primary health care

Phase 3: Pilot Trial to Evaluate the Effectiveness of eSkinHealth for Early Diagnosis and Case Management

The same local health care providers as in phase 2 will participate. They will register patients suspected of the targeted skin NTDs (Buruli ulcer, leprosy, yaws, scabies, and lymphatic filariasis) who provide an informed consent during active case finding and during consultation at PHC throughout the trial period on the eSkinHealth app platform. Clinical data at the time of initial identification and at every follow-up visit until cure will be entered in eSkinHealth, including the photos of their skin lesions. The data will be uploaded when connected to the internet and integrated into one database server. When in need of a consultation, a request will be sent to remote experts/dermatologists in Côte d'Ivoire or members of the global health dermatology community, and advice or a clinical confirmation will be provided. As for the control arm, they will diagnose and manage the cases with skin NTDs as usual following the national standard guidelines. Reporting cases from the control arm will be done by paper-based reports using the consultation registry of the Ministry of Health and the skin NTD reporting forms of the World Health Organization [25].

Outcome Measurement

For phase 2, we will use a validated questionnaire (SUS). The outcome measurement is an average of the SUS score. Bangor et al [26] found that the SUS was highly reliable (α=.91) and useful over a wide range of interface types [27,28]. The SUS consists of 10 statements with responses in the form of a 5-point Likert scale (eg, 1: strongly disagree; 5: strongly agree). According to Bangor et al [27], a SUS score above 68 would

be considered above average. In addition, a SUS score above an 80 is considered excellent and places the product in the top 10% of products tested [29]. We will use the French language version of the SUS. We will assess the usability at baseline, the midpoint (6 weeks), and the end of the study (12 weeks). In-depth interviews will be performed at the end of the study.

For phase 3, differences in case numbers diagnosed and the early detection and follow-up between the intervention group (diagnosis with the app) and the control group (usual diagnosis) will be measured as the primary outcome of this study.

Data Collection

All survey data will be obtained by study staff. We will use validated and study-specific instruments for data collection in person at enrollment, the midpoint (week 6), and the end point (week 12); the SUS and semistructured interviews will assess the usability of the app and portal. For storage of data, we have been using the Amazon S3 (Simple Storage Service) of the Amazon Web Service server, which offers a safe, secure, highly durable storage infrastructure with continuous backups, regulated under the US Health Insurance Portability and Accountability Act. Only the study team and those registered with the eSkinHealth app system (eg, nurses at primary health care clinics) will have access to data. All paper documentation including the signed consent forms will be stored in a secure cabinet, and access will be available only to the study staffs approved by the institutional review board (IRB).

Statistical Analysis

Sample Size Estimation

As for patients, a convenience sample (N=1320) of participants eligible to participate in this pilot study will be recruited. Sample size calculations were not conducted, as this is a pilot trial. The sample size of 1320 was selected based on the number of participants that could be conveniently recruited and tested within the pilot study time frame. From our previous studies, the average number of patients that got registered to the eSkinHealth app was approximately 10 per PHCs per month.

As for local health care providers, 44 local health care providers (22 local health care providers per group) will be recruited for this study. A power analysis was performed using G*Power 3.1.9.6. An estimated medium effect size of Cohen *f* 0.25 was used to determine the sample size needed for a repeated-measures multivariate analysis of variance (RMANOVA) with three time points and two groups. With 95% power (1 – ß), a sample size of 44 local health care providers is needed to detect the hypothesized medium-sized effects on the various outcomes. This RMANOVA would uncover all large- and medium-sized effects but no small-sized effects.

Data Analysis

Statistical analyses will be performed using Stata software (version 16, StataCorp). The threshold for statistical analyses will be set at $P<.05$ in a 2-tailed test. We will summarize the baseline data by group assignment using descriptive statistics: means and SDs will be used for continuous data with normal distribution, medians and IQRs for skewed data, and percentages for categorical data. Our primary outcome, number of diagnosed and early detection will be assessed by mix model analysis of variance, with intervention assignment as a between-group factor and time as a within-subject factor. As for continuous data, we will compare the data between control and intervention group using the *t* test or the Wilcoxon Mann-Whitney test. For categorical data, we will compare the data using the chi-square test.

Ethics Approval

Procedures of our methods have been reviewed and approved by the IRB of the Ministry of Health, Côte d'Ivoire (No. IRB000111917) and by the Tulane University (IRB 2020-2054-SPHTM). This study is registered at ClinicalTrials.gov (NCT05300399).

Results

This study was funded in 2021. We started the enrollment of patients in February 2022, and data collection is currently underway. Data collection is expected to be completed in October 2022. We expect the first results to be submitted for publication in 2023.

Discussion

This paper outlines the protocol for a 3-month pilot trial for evaluating the effect of the eSkinHealth app for the early detection and management of skin NTDs. This app has been our invention, and to our knowledge, there is no other mHealth app of this kind that is developed for the collection of the clinical data of skin diseases in which it can be used both online and offline. It is also portable, and therefore, it can be used in remote communities in LMICs where skin NTDs are endemic and where infrastructure is usually very poor. In terms of teledermatology, while past attempts in using WhatsApp and other social media platforms have shown successful results to an extent [20,21], they do not offer patient health information security. Furthermore, information is exchanged on a one-time basis, and it does not offer a platform for the follow-up of patients. Our system attempts to overcome these challenges.

The outcomes of this study will be primarily assessed by the number of cases of skin NTDs diagnosed and managed using the eSkinHealth app in Côte d'Ivoire, consistent with previous studies in LMICs [30-34]. We will further evaluate it with the SUS score and in-depth interviews. We expect that the average SUS score will be above 68, and the usability of the eSkinHealth app would be considered above average. We hypothesize that the use of the eSkinHealth app will improve the early detection and management of skin NTDs.

Our study may have several limitations. First, although the app can be used offline, an internet connection is required for certain functions. Poor internet connectivity may affect our results. While we can exclude PHCs with known poor internet connectivity, this will form one of the results of our study. We therefore did not include this as our criteria in the selection of the users. Second, the SUS will be evaluated at enrollment, the midpoint (week 6), and the end point (week 12). It is unclear what the effects of the intervention would be if it were

prolonged. Lastly, this is a pilot trial involving 10 to 12 PHCs in one or two health districts, and therefore, the study findings may not be generalizable to all health districts in Côte d'Ivoire. These limitations notwithstanding, this study is the first to examine the usability and the effectiveness of the eSkinHealth app to improve the early detection and case management of skin NTDs in Côte d'Ivoire. The study will provide robust evidence of the usability and the effectiveness of the eSkinHealth app to improve the early detection and case management of skin NTDs in Côte d'Ivoire. Furthermore, given the importance of improving the early detection and case management of skin NTDs in LMICs, these results will provide a compelling rationale for infectious disease policy and decision makers regarding mHealth interventions for skin NTDs in LMICs.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Center for Scientific Review Special Emphasis Panel - Mobile Health: Technology and Outcomes in Low and Middle Income Countries (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 150 KB - resprot_v11i9e39867_app1.pdf]

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Abbreviations

IRB: institutional review board
LMICs: low- and middle-income countries
mHealth: mobile health
NTD: neglected tropical disease
PHC: primary health center or clinic
RMANOVA: repeated-measures multivariate analysis of variance
S3: Simple Storage Service
SUS: System Usability Scale

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Protocol

Exploring the Experiences and Needs of Patients With Type 2 Diabetes Mellitus in Sleman Regency, Yogyakarta, Indonesia: Protocol for a Qualitative Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic disease that can cause adverse effects if not managed effectively. The prevalence of T2DM will continue to rise every year, and data from the International Diabetes Federation show that the number of patients diagnosed with T2DM in Indonesia is predicted to increase from 10.3 million in 2017 to 16.7 million in 2045. Managing T2DM properly is a challenge for the patients because they need to implement lifestyle changes that involve the self-monitoring of blood glucose, consuming prescribed medication properly, maintaining a healthy diet, getting sufficient physical training, keeping a healthy sleeping pattern, managing stress properly, and consulting medical professionals regularly. The worldwide intervention for T2DM focuses on self-management education. The varied results in studies about interventions show that no particular intervention method can be regarded as the most effective. In Indonesia, there are limited studies on educational interventions to improve the quality of life and health of patients with T2DM.

Objective: This study aims to explore the experiences and needs of patients with T2DM in Sleman Regency, Yogyakarta, Indonesia, to develop effective self-management education.

Methods: The study will use the phenomenology method with purposive sampling to collect data. The inclusion criteria are patients in the Chronic Disease Self-Management Program at the Sleman Regency Public Health Center who are aged ≥18 years, diagnosed with T2DM for more than a year, with hemoglobin A1c levels ≤7.5% and >7.5%, capable of communicating verbally and literate in the Indonesian language, not deaf, and willing to participate. The data collection is based on the Social Cognitive Theory, which involves selecting assessment targets and analyzing personal factors, environment, and behavior that determine the knowledge, attitude, and adherence of persons with T2DM. Researchers will collect the data through in-depth, face-to-face interviews to learn about knowledge, self-efficacy, outcome expectancy, outcome experience, worry, illness belief, treatment belief, diet, physical activity, medicine intake, treatment pattern, support system, as well as ethnic and cultural influences. The results will be taken from unstructured and open-ended questions written in Indonesian according to the interview guidelines. The data analysis process will go through several stages: reading the data thoroughly; coding; sorting the categories; creating the themes; making general descriptions; and presenting the data in charts, narratives, and recorded quotations from the interviews.

Results: This study received a grant in May 2021 and gained permission from the Medical and Health Research Ethics Committee of Universitas Gadjah Mada, Indonesia, on July 1, 2021. Data collection started on August 12, 2021, and the results are expected to be published in 2022.

Conclusions: The results of this study will be used to design an educational intervention model to improve the knowledge, attitude, and adherence of patients with T2DM.

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KEYWORDS

type 2 diabetes mellitus; social cognitive theory; personal factors; environment; behavior; knowledge; attitude; adherence; HbA1c; hemoglobin A1c

Introduction

Background

The prevalence of type 2 diabetes mellitus (T2DM) worldwide is projected to increase from 463 million in 2019 to 700.2 million in 2045 [1]. This global trend makes diabetes an epidemic [2,3]. Indonesia has the 7th largest number of patients with T2DM with 10 million confirmed cases and 5.2 million undiagnosed cases [1]. T2DM contributes to 2% of the mortality rate worldwide and 6% of the mortality rate in Indonesia [4,5]. Globally in 2019, T2DM and its complications caused the deaths of around 4.2 million people aged 20-79 years. At this rate, it means that every 8 seconds, 1 person dies of T2DM, with nearly half (46.2%) of the mortality coming from the working-age population (aged <60 years). The increased mortality rate and decreased quality of life caused by T2DM and its complications affect the health and economy of the patient, family, society, and even the country's health system [1].

Managing T2DM properly is a challenge for the patients because they need to implement lifestyle changes that involve the self-monitoring of blood glucose, consuming prescribed medication properly, maintaining a healthy diet, getting sufficient physical training, keeping a healthy sleeping pattern, managing stress properly, and consulting medical professionals regularly [6]. Various problems faced by patients with T2DM include an unhealthy diet, the lack of physical activity, and poor knowledge about how the disease and treatment affect the patients' treatment and medication adherence [7]. Several factors that affect medication adherence among patients with T2DM are therapy duration; complex treatment; miscommunication between patients and medical staff; the lack of information; psychological factors; and the patients' poor perception of the benefits, security, side effects, and cost of the treatment [8,9]. The lack of adherence will increase the risk of microvascular and macrovascular complications [7,10-14]. Patient adherence to treatment is the key to successfully treating chronic diseases such as T2DM [15-18]. The lack of knowledge regarding the treatment also corresponds to poor patient adherence and causes treatment failure [19].

Another problem related to T2DM in Indonesia involves the public misperceptions about the disease and treatment. One study found several public false perceptions about T2DM [20]. Another study says that only people of high economic status can have T2DM and that people of low economic status cannot possibly have the disease [20]. People also believe that T2DM is a hereditary disease that only affects those with a family history of T2DM. Furthermore, people still believe that they could prevent T2DM if they live a traditional lifestyle and deny that an unhealthy diet and smoking can cause T2DM [20]. Some patients think that T2DM is not a serious disease because they can still do daily activities. According to some people's religious belief, T2DM is given to them by God [21]. T2DM is also considered to be bad karma and inherited from a past life as a hereditary disease. Many patients with T2DM experience stress because they cannot accept their condition [22]. Many patients have low medication adherence and prefer alternative or complementary therapy [23]. Additionally, traditional medication has become popular because people have more trust in traditional medical practitioners than modern medical practices. Additionally, they are worried about the side effects of modern medication and remain skeptical about its efficacy [24].

Social Cognitive Theory

We will use Bandura's Social Cognitive Theory (SCT) as the basis of this qualitative study plan. According to the theory, the 3 components that affect someone to change their health behavior are self-efficacy, purpose or intention, and outcome expectancy [25]. Bandura expounded human behavior in terms of triadic reciprocal causation, which refers to the causal relation of personal and cognitive factors, behavior, and environment. These 3 factors work interdependently as the defining factors with other bioecological aspects [26]. Bandura's SCT emphasized the strong connection between personal factors, behavior, and environment, supported by learning through observation [27,28]. The main elements are knowledge, social support, outcome expectancy, self-regulation, and self-efficacy [28]. SCT is highly effective in predicting and explaining patient adherence to diabetes treatment [28]. Self-efficacy is closely related to the individuals' belief in their capacity to perform certain behaviors, such as exercising [29]. However, most researchers only focus on some SCT components, namely self-efficacy and self-regulation, and ignore the other aspects [28]. One study shows that intervention on patients with T2DM using SCT can improve patient adherence to proper diet, physical activity, treatment, self-foot check, and the self-monitoring of blood glucose [30]. Another study found a similar result, showing that the intervention model using SCT could also increase physical activity and adherence to prescribed medication [31]. A systematic review revealed that the

interventions using SCT on patients with T2DM can increase patient adherence to most aspects of T2DM treatment with a total quality score of 9 out of 10 and shows a more consistent result than the interventions using other behavioral theories [32]. SCT is considered the most effective model to improve patient adherence to most aspects of T2DM treatment [30,31] and continues to be one of the theories that can be applied to arrange a comprehensive model to change behavior [28].

Aim and Research Questions

This study will explore the experiences and needs of patients with T2DM in treating T2DM by analyzing personal factors, environment, and behavior.

The following 2 questions will be addressed:

1. What are the experiences of patients with T2DM in managing their disease?
2. What are the needs of patients with T2DM in managing their disease?

Methods

Study Approach

The study will use the phenomenology approach to describe human experiences about a certain phenomenon [32]. We chose phenomenology because this approach is a research strategy used to identify the nature of human experiences regarding the meaning of life as perceived by patients with T2DM. Understanding human experiences makes phenomenology a research method with procedures that require the researchers to analyze the subjects by getting involved directly for a relatively long time to develop the patterns and connections of meaning [32,33]. In this process, the researchers must set personal experiences aside to understand the experiences of patients with T2DM in bringing meaning to their lives. We intend to gain a complete understanding of the patients' knowledge, attitude, and adherence and the barriers they encounter.

Participants

The study participants will be patients in the Chronic Disease Self-Management Program at the Sleman Regency Public Health Center, Yogyakarta, Indonesia, who are aged ≥18 years, diagnosed with T2DM for more than a year, receiving oral medication therapy and not using insulin, have hemoglobin A_{1c} levels ≤7.5% and >7.5%, capable of communicating verbally and literate in the Indonesian language, not deaf, and willing to participate in the research.

Participant Recruitment

The participants will be identified according to the data provided by the Sleman Regency Public Health Center after obtaining the research permit. Subsequently, the participants will be selected according to the criteria stated above. We will hold activities in collaboration with the public health center and public health cadres. Public health cadres are community members who are selected and trained by the community health center to improve public health. Through these cadres, the candidates (patients in the Chronic Disease Self-Management Program diagnosed with T2DM) will be identified. Once all of the requirements are fulfilled, we will choose the candidates to participate in the in-depth interviews.

Sampling

Qualitative research focuses on depth and process; hence, only a relatively small number of participants (less than 10 people) will be examined in this phenomenological study. The participants will be selected using the purposive sampling technique. The sample will be considered sufficient once the obtained information reaches data saturation or data satisfaction, which refers to the point where no new information can be discovered from additional participants.

Participant Compensation

Upon the completion of the procedure, each participant will receive Rp 100,000.00 (US $6.77) as a token of appreciation for participating in the research.

Interview Procedure and Data Collection

The data collection components in this research will be interviewers (researchers and field assistants), interview guidelines, field notes, a recorder, and a camera. The research guideline for interviewing patients with T2DM will emphasize the following aspects: knowledge, self-efficacy, outcome expectancy, outcome experience, worry, illness belief, treatment belief, diet, physical activity, medicine intake, treatment pattern, support system, as well as ethnic and cultural influences. Data collection will be done through in-depth interviews, which requires conducting a face-to-face meeting. This type of interview uses unstructured and open-ended questions compiled according to the guidelines to gain insights and opinions from the participants. The time allocated for each participant in 1 meeting will be at least 60-90 minutes. The field note method will be used to document nonverbal information such as date, time, location, and the process description of the interview.

Analysis Plan

Once the data have been gathered from the participants, it will be organized and prepared for analysis and then typed and sorted into different categories. The data will be read and its meaning reflected upon to thoroughly to understand the participants' responses. In this process, we will also write several notes regarding the data. The second step will be to conduct deeper analysis through data coding, which includes processing material or information into text, extracting, and sorting them into several categories. These categories will be labeled with specific terms based on the participants' responses. The categories and themes will then be analyzed to narrow them down to a few themes or categories. These themes will be the main result of the qualitative research, which will later create a more complex analysis, becoming a general description. The third step will involve describing the themes and representing them in narratives or qualitative reports. This narrative covers the explanation about event chronology, certain themes (along with the subthemes, specific illustrations, perspectives, and quotations), or interconnections between themes. Lastly, we will interpret the data based on the questions given to the participants and their responses to gain the essence of their ideas. This interpretation will later become the meaning that

comes from the participants' experience, which aligns with the aim of this study—discovering the participants' meaning of life. This interpretation will not be our conclusion but rather the participants' ideas in their own words. Upon the completion of the analysis, the data will be presented in charts, narratives, and recorded quotations from the interview.

Ethics Approval

Approval for the study's ethics was received from the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (KE/FK/0747/EC/2021).

Results

This study received a grant in May 2021 and gained permission from the Medical and Health Research Ethics Committee of Universitas Gadjah Mada, Indonesia, on July 1, 2021. Data collection started on August 12, 2021, and the results are expected to be published in 2022.

Discussion

Expected Findings

This study aims to examine the experiences and needs of patients with T2DM in treating the disease. The data in this study will be analyzed using SCT, which involves personal factors, behavior, and environment. According to the SCT, the details gathered from the patients should include knowledge, self-efficacy, outcome expectancy, outcome experience, worry, illness belief, treatment belief, diet, physical activity, medicine intake, treatment pattern, support system, as well as ethnic and cultural influences. The study results will be used to create and develop an educational intervention model tested on patients with T2DM. Hopefully, with a proper educational intervention model, the medication knowledge, attitude, adherence, and hemoglobin A_{1c} levels of patients with T2DM can be improved.

Conclusions

The results of this study will be used to design an educational intervention model suitable for patients with T2DM to improve their knowledge, attitude, and adherence.

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Authors' Contributions

YL developed the study protocol, prepared the data collection tools, conducted primary data collection and analysis planning, and wrote the draft paper. EK, YSP, and SAK supervised the study, reviewed the paper, and provided substantial input. All authors have approved the manuscript for submission.

Conflicts of Interest

None declared.

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Abbreviations

SCT: Social Cognitive Theory
T2DM: type 2 diabetes mellitus

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Corrigenda and Addenda

Correction: Awareness, Information-Seeking Behavior, and Information Preferences About Early Childhood Allergy Prevention Among Different Parent Groups: Protocol for a Mixed Methods Study

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In "Awareness, Information-Seeking Behavior, and Information Preferences About Early Childhood Allergy Prevention Among Different Parent Groups: Protocol for a Mixed Methods Study" (JMIR Res Protoc 2021;10(1):e25474), the authors noted one error.

1. In the originally published article, the *Acknowledgments* section inadvertently appeared with an incomplete funding statement as follows:

> *We would like to thank Reuben Thomas very much for detailed language support. We would also like to thank the initial members of the research group HELICAP [66], funded by the German Research Foundation, of which this project is a part: Christian Apfelbacher, Eva Maria Bitzer, Uwe Matterne, Nina Egger, Janina Curbach, Julia von Sommoggy, Susanne Brandstetter, Maja Pawellek, Carolin Dresch, Anja Schulz, and Markus Wirtz. We would also like to thank the external grant proposal advisors—Julika Loss and Kristine Sørensen—and the grant proposal reviewers who all provided valuable and critical feedback on the conceptualization of the study, its methodological design, and its integration into the overarching goals and structure of the research group.*

In the corrected version, the *Acknowledgments* section has been updated as follows:

> *We would like to thank the steering committee (Christian Apfelbacher, Eva Maria Bitzer, Janina Curbach, Marie-Luise Dierks, Susanne Brandstetter, Markus Antonius Wirtz) as well as the initial members (Nina Egger, Christina Tischer, Jana Tempes, Uwe Matterne, Julia von Sommoggy, Maja Pawellek, Carolin Dresch, Anja Schulz) of the research group "Health Literacy in Early Childhood Allergy Prevention" (HELICAP, [66]). HELICAP is funded by the German Research Foundation (DFG FOR 2959, project-id: 409800133), of which this project is a part (grant number: DI 1757/2-1). The funder had no role in the design of the study, data collection, data analysis, or interpretation of the results. We also thank the external grant proposal advisers (Julika Loss, Kristine Sørensen) and the grant proposal reviewers who all provided valuable and critical feedback on the conceptualization of the study, its methodological design, and its integration into the overarching goals and structure of the research group. Lastly, we are grateful for the detailed language editing support provided by Roy Reuben Thomas.*

The correction will appear in the online version of the paper on the JMIR Publications website on September 9, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Examining the Development of Information Needs Assessment Questionnaires in Oncology: Protocol for a Scoping Review

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Abstract

Background: Information needs are one of the most prevalent unmet supportive care needs of those living with cancer, including patients and their informal caregivers. Understanding how existing questionnaires for evaluating information needs have been developed is important for guiding appropriate use and informing future research. A literature review examining how information needs assessment questionnaires for use in the cancer context have been developed, with a specific focus on how questionnaire items have been identified, does not exist.

Objective: This scoping review will examine how questionnaires for assessing the information needs of those living with cancer have been developed with special focus on how patients, informal caregivers, and health care professionals have been involved in the selection and identification of questionnaire items.

Methods: This review will include published studies describing the development and validation of information needs assessment questionnaires for use in the oncology context. MEDLINE (Ovid), Embase (Ovid), CINAHL, Scopus, Web of Science, the Cochrane Database of Systematic Reviews, and PsycInfo will be searched. Articles published at any point up to the date of the search will be eligible for inclusion. One person will screen titles and abstracts, and 2 people will screen and extract data from full-text articles.

Results: Results are expected to be available in early 2023. Summary tables and a narrative summary will be used to describe results.

Conclusions: This scoping review will assist in identifying appropriate information needs assessment tools to incorporate into clinical and research contexts in oncology. It will also identify if additional information needs assessment tools are needed.

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KEYWORDS

information needs; cancer; patient-oriented research; psychometric; measure; questionnaire; oncology

Introduction

Overview

Information needs are one of the most commonly unmet supportive care needs of patients and informal caregivers (ie, friends and family who provide unpaid support to patients) [1]. Information plays an important role in both emotional and problem-based coping [2]. When faced with a health problem such as a new diagnosis of cancer, individuals seek information to help them adjust and understand what actions they can take to improve their situation both in the short and long term. When information needs are addressed, patients are more likely to be active participants in decision-making [3], have better health-related quality of life, and lower rates of anxiety and depression [4,5].

Information needs of patients with cancer and their informal caregivers have been assessed in multiple studies, using validated questionnaires [6,7]. Validated questionnaires provide researchers with tools that have been rigorously developed [8] and produce data that can be compared between populations and across time. However, when assessing information needs using a validated questionnaire, it is important to understand how the questionnaire was developed and its intended use. Inappropriate selection of questionnaires can lead to erroneous conclusions and recommendations [8].

One important consideration when selecting a questionnaire is how the questionnaire items were identified. Regarding information needs, at least on a theoretical level, an important distinction is between normative and expressed information needs [9]. The word “normative” [2] has been used to describe the information needs identified by health care professionals as important for health care recipients to know. In contrast, “expressed” [2] needs refer to information needs that are identified as important by health care recipients such as patients with cancer and their informal caregivers. Although there is likely an overlap between normative and expressed needs, it is hypothesized that key differences are also likely to exist both in the content of these different types of information needs and the consequences of whether or not each type of information need is met.

Normative information needs may, at least to some degree, be influenced by the pressures that health care professionals face in their respective clinical, research, and administrative roles. On the other hand, expressed information needs may be more likely to reflect day-to-day challenges of those living with cancer, as they continue to pursue their prediagnosis value-based goals [9-11], while navigating a cancer diagnosis, survivorship, and a health care system with its own goals and values. The crux of the distinction is that, at least theoretically [9], an educational intervention designed to address normative information needs may facilitate a patient fitting well within the health care system, whereas targeting expressed needs may facilitate health care fitting better with the patient’s life and values. If this is true, when selecting or interpreting the results from a questionnaire designed to assess information needs, it is important to have a clear understanding of whether the questionnaire is assessing normative or expressed information needs. This likely requires an understanding of the intended use of the questionnaire, the steps involved in its development, how it was validated, and the processes involved in identifying the questionnaire items, including how health care recipients, informal caregivers, and health care professionals were involved in questionnaire item generation and selection.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, *JBI Evidence Synthesis*, and PROSPERO was conducted to identify previous systematically conducted literature reviews exploring how information needs assessment tools in oncology were developed. This search identified systematic reviews of information needs in the cancer population that included studies using validated information needs assessment tools to describe the information needs of patients with cancer [6,7]. Additionally, one review by Christalle et al [12] was identified that had systematically reviewed information needs assessment tools across the health care spectrum, including in the cancer context. However, similar to other reviews of health needs assessment tools [13,14], this review focused on the methodological quality and psychometric properties of the tools. A review specifically exploring how questionnaire items were identified and selected and who was involved in this process could not be identified. Therefore, a review is needed that is specific to the cancer context, characterizing how information needs assessment questionnaires have been developed, their intended use, and whether the types of information needs being assessed are likely normative, expressed, or both. The preliminary review performed as part of the development of this protocol supports that there are adequate numbers of information needs assessment questionnaires used in contemporary cancer research to provide data for this review as evidenced by the 11 oncology-specific questionnaires identified in the review by Christalle et al [12].

This review will use a scoping review approach. A scoping review is the most appropriate method for examining how information needs assessment tools in the oncology context have been developed. Scoping reviews are a rigorous approach to knowledge synthesis and are also flexible and can be used to address a number of different types of objectives, including mapping the literature and describing how research has been conducted [15,16]. This contrasts with systematic reviews, which are best suited for research questions related to clinical practice, where a comprehensive and unbiased summary of the literature is required [15,17,18], such as when results from randomized controlled trials are being compared to determine best practices.

The objective of this scoping review is to examine how the existing tools for assessing information needs of patients with cancer and their friends and family have been developed, including how they have incorporated expressed information needs. This will be achieved by systematically reviewing the literature to comprehensively identify information needs assessment tools developed for the cancer context and then examining how they have been developed and validated. The rationale for the development of each questionnaire as well as the processes for identifying, finalizing, and validating the questionnaire will be described. Regarding expressed information needs, the role of the patients and informal

caregivers in identifying potential questions and needs domains as well as determining the final version of the assessment tool will be summarized.

Review Questions

The objectives of this review will be achieved by systematically reviewing the literature to answer the following questions:

- What questionnaires have been created and validated for evaluating the information needs of people living with cancer?
  - What is the stated purpose of each questionnaire?
  - What cancer contexts (ie, cancer type, treatment intent, and population) have these tools been developed for?
- How were the questionnaires developed?
  - How were potential questionnaire items identified and finalized?
  - How were the questionnaires validated?
  - How were patients, health care professionals, and informal caregivers involved in the process of developing the questionnaires, including in the identification and selection of questionnaire items?
  - How were test and measurement guidelines (eg, COSMIN checklist [19]) used in the development and reporting of the measure?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [16,20]. The one exception to this is that the screening of titles and abstracts will be conducted by a single author, as supported by Cochrane [21].

Eligibility Criteria

Population

This scoping review is focused on characterizing the development of validated assessment tools rather than characterizing differences in measured outcomes in certain populations. As such, the "participants" aspect of the scoping review eligibility criteria is not applicable.

Concept

This scoping review will examine how information needs assessment tools have been developed, including the motivation for the development, the steps in the development, and the steps taken to include the expressed information needs of health care recipients.

Context

This scoping review will include the literature relevant to the cancer context, both in clinical and research settings. It will include published reports describing the development of tools designed for patients and/or informal caregivers (ie, friends and family). Literature specific to the pediatric population will be excluded. Non–English-language studies will be excluded.

Types of Sources

This scoping review will consider any report related to the development of information needs questionnaires for patients with cancer published in peer-reviewed journals. Reports will include those that directly describe and report on their development, including methods of identifying questionnaire items as well as testing of psychometric properties. Additionally, reports cited as rational for selection of certain items will be included. As a result, this review will include a wide range of reports including but not limited to the following: protocols of both experimental and quasi-experimental study designs such as randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time series studies; analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies; descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies; experimental studies; reports on preliminary results and works in progress; qualitative studies; systematic reviews; and peer-reviewed essays and opinion papers.

Search Strategy

The search strategy will aim to locate both published and unpublished studies related to the development of information needs assessment tools for the oncology context. An initial limited search of MEDLINE (Ovid) and CINAHL Plus with Full Text was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used, in collaboration with a health sciences librarian, to develop a full search strategy for MEDLINE (Ovid) and CINAHL (Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database or information source. The databases to be searched include MEDLINE (Ovid), Embase (Ovid), CINAHL, Scopus, Web of Science, the Cochrane Database of Systematic Reviews, and PsycInfo.

Studies published in English will be included. Non–English-language studies will not be included as the researchers are primarily interested in learning what tools are available for use in their respective English-based clinical and research practices. Studies published since the beginning of the database will be included, as there is no reason to exclude older studies.

As appropriate, authors of reports will be contacted to determine if missing or additional data are available in peer-reviewed publications. Grey literature, and non–peer-reviewed reports, including unpublished studies or protocols, will not be excluded from this review. Inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for search strategy.

Inclusion criteria

- Reports indexed up to the date when article searching begins (ie, post completion of blind protocol peer review).
- Reports describing the development or use of information needs assessment questionnaires, specifically for adults living with cancer, including patients and informal caregivers.
- Reports related to any type of malignancy, including a single or multiple types.
- Reports related to any point in the cancer journey, from diagnosis to surveillance or palliation.
- Any geographic location.

Exclusion criteria

- Non–peer-reviewed literature.
- Non–English-language literature.
- Reports related to the development of multidimensional needs assessment tools (ie, not focused on information needs).
- Reports related to tools designed specifically for the pediatric population, including adult informal caregivers of patients with pediatric cancer.
- Reports related to assessing information needs regarding cancer screening.

Evidence Selection

Following the initial database search, all identified citations will be collated and uploaded into Covidence (Veritas Health Innovation), and duplicates will be removed. Titles and abstracts will then be screened by 1 independent reviewer for assessment against the inclusion criteria for the review [21]. The full text from the screened articles will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for the exclusion of full-text sources of evidence that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer(s). The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews) flow diagram [22].

Data will be extracted from papers identified through the search strategy by 2 independent reviewers, using a data extraction tool developed by the reviewers. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions.

A draft extraction form is provided (Multimedia Appendix 2). It was initially developed from the template provided by JBI for data extraction tools used in scoping reviews [16] and informed by the research questions. In particular, specific data extraction questions focused on identifying the level of involvement of patients and informal caregivers, compared to health care professionals, will assist in evaluating whether the questionnaire is focused on assessing expressed or normative information or a balance of both, or if it is simply not clear from available literature. Additionally, the COSMIN checklist sections related to general recommendations and content validity were used to inform the development of the data extraction tool [19], as they closely relate to the objectives of this study.

The draft data extraction tool will not be piloted prior to data extraction. However, the extraction tool is expected to be modified and revised during the process of extracting data to capture relevant data, including data that emerges as important during the course of data extraction. Modifications to the extraction tool will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or via additional independent reviewers.

Of note, to ensure that the number of information needs assessment tools reviewed in this study is as comprehensive as possible, the titles and abstracts identified through the initial database search will also be reviewed to identify studies reporting on quantitative assessments of information needs using validated questionnaires. Screening for these articles will be accomplished by a single reviewer who will also review the full text of these studies, including their references lists, to identify additional reports potentially meeting the inclusion criteria of this scoping review. These articles will be combined with other articles selected for full-text review to meet inclusion criteria, and from that point, they will be treated equally with articles identified directly through the database search. The number of articles identified through this process will be clearly demarcated in the PRISMA-ScR flow diagram.

Results

Activities related to this scoping review began in December 2021 with the drafting and submission of this protocol for peer review and publication. Results are expected to be available in early 2023 and will be reported in accordance with the PRISMA-ScR reporting guidelines [22]. Extracted data will be presented in both narrative and table forms. A summary table of the year of publication, country of the lead author, and cancer contexts (ie, treatment intent, type of cancer, and during active treatment or surveillance) for which the questionnaires were developed will be created. Additionally, 2 separate tables will be created summarizing the collected data related to the first and second research questions.

Discussion

Principal Findings

Based on the preliminary search conducted as part of the development of this protocol, the resulting scoping review will be the first to systematically evaluate the development of information needs assessment questionnaires for use in the oncology context. Importantly, it will characterize how the expressed needs of those living with cancer have been incorporated into the existing information needs assessment tools. As such, this review has the potential to impact both clinical and research practices in oncology, including but not limited to the development of more rigorous patient-reported measures in oncology settings.

In the clinical setting, this review will be helpful in guiding tool selection for capturing information needs in routine practices. Screening for psychosocial distress as part of the routine oncology clinical practice is considered standard of care by many professional organizations such as the American Society of Clinical Oncology [23]. Routinely, patient-reported outcome measures (PROMs) are central to distress screening strategies. In some institutions, PROMs that specifically assess information needs are collected as part of a routine practice [24]. By being the first systematically conducted review to characterize whether existing information needs assessment tools developed for the cancer context assess normative versus expressed information needs, this review will inform clinicians in identifying which information needs questionnaires to include as part of their routine assessments. Additionally, it will assist clinicians in the correct interpretation of results, which may lead to better identification of information gaps and development of improved information provision practices.

From a research perspective, this review is expected to support researchers in identifying appropriate tools for capturing information needs–related data and facilitating awareness of the limitations of the selected tools [8]. It will also identify where there is a need for development of additional measures and provides insight into best practices for the development of information needs measures in the future. Lastly, by identifying how the expressed information needs [2] of those experiencing cancer have been included in existing measures, this review will provide an important lens for interpreting the existing published literature characterizing the information needs of those living with cancer.

Limitations

Despite identifying what appears to be an adequate body of literature to support this review, it is not clear whether sufficient details will be able to be identified in the existing peer-reviewed literature to adequately address the research questions. Although the rate of publication of protocols is increasing [25], research results, including descriptions of the research methods employed, commonly go unpublished [26]. It is simply not known whether a sufficient level of detail about the procedures used to develop the instruments to answer the research questions will be identified in the peer-reviewed literature. Identifying the relative presence or absence of the details relevant to the research questions in the literature is not an explicit objective of this review; however, the discovery of insufficient data to address specific research questions will certainly be important for guiding future work such as in-depth qualitative explorations of how existing questionnaires have been developed incorporating semistructured interviews with the lead developers.

Conclusions

Information needs are one of the most commonly unmet supportive care needs of those living with cancer [1]. Unmet information needs negatively impact the cancer experience [3-5]. Understanding how the questionnaires used to assess the information needs of those living with cancer have been developed is key to appropriate questionnaire selection and interpretation of reported results [8]. Systematic literature reviews exploring various aspects of information needs questionnaires exist [13,14], and they have included tools specific to oncology [12]; however, a review is needed to specifically explore how information needs assessment questionnaires in the oncology context have been developed. This review will address this gap in the literature, and in doing so, assist future work to better support those living with cancer.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample search strategies.
[DOCX File , 16 KB - resprot_v11i9e35639_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 20 KB - resprot_v11i9e35639_app2.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews
PROM: patient-reported outcome measure

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Protocol

Shared Learning Utilizing Digital Methods in Surgery to Enhance Transparency in Surgical Innovation: Protocol for a Scoping Review

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Abstract

Background: Surgical innovation can lead to important improvements in patient outcomes. Currently, information and knowledge about novel procedures and devices are disseminated informally and in an unstandardized way (eg, through social media). This can lead to ineffective and inefficient knowledge sharing among surgeons, which can result in the harmful repetition of mistakes and delay in the uptake of promising innovation. Improvements are needed in the way that learning in surgical innovation is shared through the development of novel, real-time methods, informed by a contemporary and comprehensive investigation of existing methods.

Objective: The aim of this scoping review is to explore the application of existing digital methods for training/education and feedback to surgeons in the context of performing invasive surgical procedures. This work will (1) summarize existing methods for shared learning in surgery and how they are characterized and operationalized, (2) examine the impact of their application, and (3) explore their benefits and barriers to implementation. The findings of this scoping review will inform the development of novel, real-time methods to optimize shared learning in surgical innovation.

Methods: This study will adhere to the recommended guidelines for conducting scoping reviews. A total of 6 different searches will be conducted within multiple sources (2 electronic databases, journals, social media, gray literature, commercial websites, and snowball searches) to comprehensively identify relevant articles and data. Searches will be limited to articles published in the English language within the last 5 years. Wherever possible, a 2-stage study selection process will be followed whereby the eligibility of articles will be assessed through the title, abstract, and full-text screening independently by 2 reviewers. Inclusion criteria will be articles providing data on (1) fully qualified theater staff involved in performing invasive procedures, (2) one or more methods for shared learning (ie, digital means for training/education and feedback), and (3) qualitative or quantitative evaluations of this method. Data will be extracted (10% double data extraction by an independent reviewer) into a piloted proforma and analyzed using descriptive statistics, narrative summaries, and principles of thematic analysis.

Results: The study commenced in October 2021 and is planned to be completed in 2023. To date, systematic searches were applied to 2 electronic databases (MEDLINE and Web of Science) and returned a total of 10,093 records. The results of this scoping review will be published as open access in a peer-reviewed journal.

Conclusions: This scoping review of methods for shared learning in surgery is, to our knowledge, the most comprehensive and up-to-date investigation that maps current information on this topic. Ultimately, efficient and effective sharing of information and knowledge of novel procedures and devices has the potential to optimize the evaluation of early-phase surgical research and reduce harmful innovation.

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Introduction

Background

Surgical innovation is common and plays a crucial role in advancing surgical practice. It is characterized by a developmental process whereby novel procedures and devices evolve from early ideas and first-in-human studies to longer-term evaluations. Surgeons acquire important learning from incremental cases [1-3], leading to a steep learning curve in the early phases of technique development. Transparent sharing of case-by-case learning is therefore critical to promote efficient and safe innovation and timely evaluation of surgical innovation when a new technique has stabilized [2,4].

Currently, surgeons tend to innovate independently. Early incremental learning, including modifications to the technique and its outcomes, is rarely shared beyond the local team, if at all. Traditionally, dissemination of information about innovative procedures occurs at a relatively late stage through surgeon innovators presenting their technique at meetings and conferences, followed by taught courses and peer-reviewed publications [1,5]. Key incremental case-by-case learning is often not recorded. Evidence in other areas has shown that the outcomes of using an innovation are positively affected when knowledge is shared between external stakeholders [6], which can even be a source of innovation itself [7]. Increased shared learning in surgical innovation may provide similar benefits.

Disseminating new knowledge in health care is known to be challenging [8]. The process of exchanging information can be influenced by a multiplicity of factors, including organizational, cultural, social, and psychological influences [9,10] and facilitated by technology [11]. More recently, surgeon innovators are increasingly utilizing digital platforms and social media to disseminate ideas and practice [12]. While this has notable benefits, the acquired knowledge is shared inconsistently [13,14]. It may promote optimism bias by preferentially favoring positive developments and outcomes and is unsuited to building a robust evidence base [15]. Furthermore, approaches to disseminating information provide little or no scope for feedback, hindering efficient innovation that can address learning curve effects. This may also mean the benefits and harm outcomes of innovation are underreported or not shared transparently, and opportunities to promote patient safety by avoiding repetition of potentially harmful mistakes are therefore lost. Methods for effectively and transparently sharing information in real time are needed to accommodate incremental, case-by-case learning when developing a new surgical technique. Such methods must also include mechanisms for the confidential provision of feedback to avoid patient harm while simultaneously ensuring a safe space for surgical innovation.

A number of digital methods to provide feedback exist, including image analysis [16], artificial intelligence [17], or virtual and telementoring platforms [18]. These have been demonstrated to improve outcomes relevant to patients (eg, reduced operative time) and surgeons (eg, improved surgical skills) for established procedures [19,20]. It is therefore possible that similar methods could be used or adapted to capture the incremental learning associated with an innovative surgical technique in near real time. Digital methods may also enable prompt sharing to facilitate efficient, transparent, and safe innovation of novel surgical procedures.

There is no standard definition of surgical innovation, and descriptions of novelty vary considerably across the literature [21,22]. Identification of relevant literature on surgical innovation is also hindered by poor reporting [4,23,24]. Innovations are “frequently reported as information communications which may not be well organized and are sometimes anecdotal“ (pg 1) [25]. Standard systematic review methodology would therefore be unlikely to identify relevant studies consistently and reliably. A literature synthesis that adopts a broad approach to include a wide variety of publication types is required to capture a range of digital methods for shared learning in surgery in general. Initial scoping searches (using Google) showed no such review has been conducted. A scoping review is considered a suitable approach for mapping a complex topic area where no prior investigation exists [26-28]. Methods allow inclusion of a range of study designs without requiring a formal quality assessment of the included articles. A scoping review of currently available methods used to share learning in surgery can identify potentially relevant digital methods, which in turn can inform the development of novel methods to optimize shared learning in surgical innovation.

Aims and Objectives

The aim of this scoping review is to explore the application of digital methods for training/education and feedback for shared learning in the context of invasive surgical procedures. We aimed to:

1. Summarize existing methods for shared learning (ie, digital methods for learning or education *and* feedback) and how they are characterized and operationalized

2. Examine the impact of the applications of methods for shared learning from data on the evaluation of methods
3. Explore benefits and barriers to the implementation of methods for shared learning from data on the evaluation of methods

Results will inform strategies for embedding suitable methods within an electronic platform for real-time reporting and sharing of outcomes of surgical innovation.

Methods

Overview

A scoping review was chosen to investigate this topic due to the breadth and type of the data of interest for the research question. This scoping review will be conducted adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping reviews (PRISMA-ScR) and established frameworks for conducting scoping reviews [26,28-30]. An initially completed checklist can be found in Multimedia Appendix 1 [28], and an updated checklist will be provided upon publication of results. Two trained reviewers will conduct the review, with input from a multidisciplinary team consisting of surgeons, methodologists, health services researchers, and social scientists. Any necessary deviations from the current protocol will be reported in the completed manuscript.

Ethical Considerations

Ethical approval for this scoping review was not required, because it does not involve human participants, their tissue, data or samples or has ethical implications, as outlined in institutional policies including Section 2 of the University of Bristol's Ethics of Research Policy and Procedure.

Definitions

Shared Learning

There is no consensus definition of shared learning in the health care or surgical literature [31]. For the purposes of this review, we have defined shared learning as a method of providing training/education with feedback to 2 or more clinicians undertaking surgical procedures. Examples of training or education and feedback in surgery can include but are not limited to assessment of skills; performance or outcomes; proctorship, mentoring, apprenticeships; and demonstration of techniques and simulation.

Digital Methods

Digital methods will be defined as utilizing electronic technology that is able to generate, store, and process data. In this review, we will exclude any methods that are used in situ (eg, laparoscopic equipment that includes cameras to broadcast to screens located in the operating theater).

Invasive Procedure

An invasive procedure is defined as "one where purposeful/deliberate access to the body is gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice. It begins when entry to the body is gained and ends when the instrument is removed, and/or the skin is closed. Invasive procedures are performed by trained healthcare professionals using instruments, which include, but are not limited to, endoscopes, catheters, scalpels, scissors, devices and tubes" (pg 2) [32].

Surgical Innovation

There is no agreed definition of innovative surgical innovation [21,22,33] and no validated methods to identify the phase of evaluation retrospectively in the published literature. Innovative surgical procedures were therefore defined as those where authors self-report an invasive procedure as "new" or "modified," corresponding to phases 1, 2a, and 2b of the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework [34,35].

Identifying Relevant Articles

Data Sources

Scoping searches conducted to inform our study have confirmed that relevant information is contained in a variety of data sources beyond traditional peer-reviewed publications. A number of different data sources are proposed to be of value for navigating the unique landscape of available evidence and addressing the study aim (Table 1).

Table 1. Publication types considered in this review, with examples of possible data sources.

Publication type	Possible data sources (examples)
Peer-reviewed publications	Protocols, conference abstracts, empirical studies of any publication type (eg, pilot, feasibility, methodological, diagnostic accuracy, intervention, and observational studies)
Opinion pieces	Editorials, comments, letters, perspectives, news, bulletins
Social media	Twitter posts, YouTube videos
Gray literature	Scientific, academic, government, or commercial reports (eg, reports of artificial intelligence or virtual reality systems)
Commercial online resources	Websites of manufacturers and platform/software/hardware providers related to training/education and feedback systems (eg, Johnson & Johnson, Medtronic, Proximie, Explorer Surgical, Visual Lab 360, Kognito, Oxford Medical Simulation, and Immersive Touch)

Searches

A total of 6 approaches will be followed to identify relevant data sources detailed above. Collaboration with a subject librarian will aid optimization of searches and inclusivity of search terms throughout.

Electronic Database Searches

A comprehensive search strategy for conducting electronic database searches will be developed. Keywords will be based on the study eligibility criteria using the search strings "shared learning" AND "methods" AND "invasive procedures." Targeted internet searches and relevant existing search strategies (eg, for invasive procedures [32]) will be used to inform the list of keywords. Search strategies can be found in Multimedia Appendix 2.

The search strategy will be translated to search for relevant publications in MEDLINE (Ovid version) and Web of Science.

Journal Searches

Scientific journals that are likely to publish relevant papers will be searched manually to identify any peer-reviewed articles that may be missed through electronic database searches. Contents pages of journals will be reviewed with a date of publication within the last 5 years. Journals of interest will be identified through expert knowledge and journal databases (eg, Web of Science Master Journal List). Relevant journals identified a priori include *Journal of Medical Internet Research*, *BMJ Surgery, Interventions & Health Technologies*, *Surgical Innovation*, *Health Information Research*, *Methods of Information in Medicine*, and *Applied Clinical Informatics*. Additional journals from previously identified articles will be added as appropriate.

Social Media

Social media platforms Twitter and YouTube have been identified as common sources for sharing knowledge about surgical innovation [36] and will therefore serve as an additional data source to inform the extent of their utility. Multiple different methods for querying social media platforms exist with known advantages and limitations [37]. Information will be searched by entering keywords related to "surgery" (eg, surgical, procedure) and "innovation" (eg, novel, improved, recently developed, adapted) into the social media platforms' own advanced search functions (eg, Twitter application programming interface). These functions are free to use, providing access to 1% of real-time content. Automated dashboard vendors provide licensed software for the retrieval and analysis of social media content (eg, Mediatoolkit, Radian6). Dashboard vendors provide access to the full content of posts across a range of social media platforms. They will be considered to supplement searches if social media posts identified through advanced search functions are considered insufficient. The same keywords will be used and combined with Boolean search operators to retrieve relevant content.

Gray Literature

A search of the gray literature will be conducted to identify potentially relevant articles not indexed in electronic databases. Specific sources to search for gray literature include OpenGrey, Canada's Drug and Health Technology Agency's Gray Matters, Healthcare Management Information Consortium, National Technical Information Service, and American Psychological Association PsycExtra, and internet searches (eg, using Google). Simple search terms will be used for these searches and adjusted based on gray literature sources and results. Any adjustments, if necessary, will be reported in the final manuscript.

Handsearching of Commercial Websites

Websites of commercial providers of digital platforms or software that are known to the research team will be searched to identify further relevant information on digital methods for shared learning. Relevant websites of known surgical technologies and technology providers will include but are not limited to Proximie, Explorer Surgical, Visual Lab 360, Kognito, Oxford Medical Simulation, Touch Surgery, Immersive Touch, Johnson & Johnson, and Medtronic. Commercial providers that do not have product-ready solutions or are currently still in development and/or lack relevant publicly available data will be excluded.

Snowball Searches

One-layer forward snowball searches (citation mining) and reverse snowballing (chain searching) will be applied to all included papers to capture related publications that may fall outside of the established search strategy. Any relevant review article (including systematic, scoping, literature, and narrative reviews) identified through any of the above searches will be retrieved and their reference lists screened for further potentially eligible records.

Study Eligibility

Study eligibility criteria are defined according to the Population, Concept, and Context framework [38] and are presented in Table 2. Publications will only be considered if they are dated within 5 years of their original publication date to ensure data is contemporary. Articles will also be excluded if they are not published in the English language, due to resource restrictions that prevent the translation of non-English articles.

Table 2. Study eligibility criteria.

Element	Inclusion criteria	Exclusion criteria
Population	• Adult (>18 years) human population • Any individual qualified to undertake an invasive procedure (eg, junior doctors, surgeons, physicians, consultants, radiologists, endoscopists, gastroenterologists, cardiologists, advanced nurse practitioners)	• Individuals not qualified to undertake an invasive procedure (eg, medical students, undergraduates)
Concept	• Discuss, report, and/or evaluate one or more methods for shared learning (ie, for training/education and feedback) • Must utilize digital means for shared learning • Quantitatively or qualitatively evaluate the method for shared learning	• Focus on digital method(s) for shared learning that are solely aimed to be used in situ (eg, laparoscopic techniques that have a camera installed and broadcast inside the operating theater) • Simple descriptive presentation of the method for shared learning
Context	• Must be in the context of invasive procedures	• N/A[a]

[a]N/A: not applicable.

Study Selection

For records with common publication formats (ie, published a title, structured abstract, executive summary, or synopsis), a 2-stage screening process will be undertaken to assess records for inclusion against the study eligibility criteria.

Search results will be downloaded from their respective online databases, deduplicated, and uploaded to an online review manager (Rayyan) [39]. In a first step, 3 review authors (CH, MK, and JR) will independently (each review author will be blind to the screening choice of the others) screen the titles and abstracts, executive summaries, or synopses of the retrieved records, with 10% of records double-screened. Full texts of articles will be obtained from records meeting the inclusion criteria and from those where inclusion remains uncertain (eg, because of a lack of information from the abstract). In a second step, 2 reviewers will each screen half of the retrieved full texts independently to assess full eligibility. Duplicate assessment of eligibility will be performed on 10% of all full texts with further duplicate reviews in case of poor agreement (<80%).

It is anticipated that some potentially relevant records do not follow conventional publication formats (eg, tweets, opinion pieces, news articles). In this case, 2 reviewers will independently review the content of the record in full.

Discrepancies at any stage of the screening process will initially be discussed between the 2 review authors. A third independent reviewer (SP) will arbitrate where agreement on inclusion could not be reached, and input from the wider team will be sought where necessary.

Data Extraction

Data extraction will be performed directly into a purposely designed electronic data extraction form (eg, Microsoft Access; Microsoft Corp). Details about (1) study and publication characteristics (eg, author, study design, funding, and sponsorship statements), (2) the method for shared learning (eg, purpose, type, operationalization, and modality), and (3) impact of methods for shared learning (eg, methodology of evaluating methods for shared learning and their results, limitations, and author recommendations) will be extracted. Additional items of interest for social media posts will be explored to capture further information on their content (eg, presence of a link to an external website). An initial data extraction form will be piloted with a small number of relevant articles (see Multimedia Appendix 3). The form will be iteratively refined to comprehensively capture all relevant detail emerging during the pilot.

One review author will extract data from all included studies, and a second reviewer will independently perform double data extraction for at least 10% of articles. Consistency in the approach to data extraction will be ensured through constant dialogue between the 2 reviewers.

Data Analysis

Findings will be summarized in tables using descriptive statistics and in narrative form. Verbatim extracted data will be analyzed by 2 reviewers adhering to principles of thematic analysis [40]. Identified themes will be displayed in schematics. Any verbatim extracted data will be reviewed to identify barriers and benefits to the implementation of shared learning methods. Barriers will be considered factors that impede the implementation of methods for shared learning in clinical practice. Benefits will be considered those that enable implementation [41]. Two reviewers will code data as a barrier or benefit, whereby regular meetings will be held to discuss coding results, and senior authors will be involved where consensus is required. In case an automated dashboard vendor is used to identify social media posts, the content will undergo additional analysis using the software's existing classification algorithms and analyses (eg, sentiment analysis).

Results

This work was initiated in October 2021. Iterative refinements to the scoping review protocol and formalizing of methods were completed in January 2021. Targeted searches were conducted in December 2021 to inform the development of a comprehensive search strategy for electronic database searches. This strategy was iteratively developed for and tested in MEDLINE. The final search was applied to MEDLINE and Web of Science in March 2022 and yielded a total of 10,093 records. Identification of relevant articles is currently ongoing and is expected to be completed by December 2022. Study

selection, data extraction and analysis, and drafting of the manuscript to report the results of this scoping review will be conducted throughout 2023. Open access peer-reviewed publication is expected in 2023. Any changes to the methods reported here will be documented and reported.

Discussion

This scoping review will explore methods for the application of digital methods for training/education and feedback for shared learning in the context of invasive surgical procedures. This work is, to the authors' knowledge, the first to (1) summarize the application of existing methods for shared learning, (2) examine the impact of their application, and (3) explore the benefits and barriers to their implementation in the context of surgery. This scoping review protocol outlines a total of 6 different approaches to identify relevant articles and data to comprehensively map currently available information on this topic.

The results will provide an investigation of contemporary methods, which will be of interest to health care professionals and methodologists wishing to adopt methods for shared learning in surgical practice. Crucially, this work will contribute to ongoing research that aims to optimize safe and transparent innovation by promoting the sharing of incremental case-by-case learning among surgeons performing new procedures. Knowledge sharing in surgical innovation has not yet received much research attention, and there may be additional challenges that need to be considered. For example, surgeon innovators may be reluctant to share ideas and might show hesitancy in light of potential impacts on confidentiality or reputation. There is currently no evidence that demonstrates the underlying mechanisms that may impact surgeon innovators' behavior toward sharing learning. This is an important avenue for future research requiring further exploration in qualitative work.

The findings from this scoping review will provide an initial step to inform the development of strategies to improve the efficiency and effectiveness of disseminating knowledge and information about novel procedures and devices. Essential to this ongoing work is the codevelopment of a real-time electronic platform that aims to collect, analyze, and feedback data about novel procedures and devices. Such an electronic platform will host a range of evidence-based approaches to safe and transparent surgical innovation that can facilitate the standardized collection and sharing of information and knowledge about novel procedures and devices [2,4]. Ultimately, enhancing shared learning in this way will reduce the risk of avoidable patient harm and streamline the evaluation of early-phase invasive procedures and devices.

This work will adhere to a robust methodology following the recommended standards for conducting scoping reviews [26,28,29]. This will ensure transparency and reduced risk of bias. Common limitations of scoping reviews, which also apply to our work, should be noted. Searches will be restricted to the English language, which limits our ability to summarize and examine findings from methods for shared learning in non–English-speaking contexts. Identifying surgical innovation and related information is hindered by poor reporting and informal dissemination. This work will intentionally address this challenge through an extensive search, but this may still not be sufficient to exhaustively capture all existing work using literature synthesis methods. Electronic database searches will be limited to 2 databases. Expert advice was sought, and it is expected that most of the relevant information on shared learning is included in these databases. However, there is a possibility that additional information of interest may be missed.

In conclusion, this scoping review will enhance our knowledge about the application of contemporary digital methods for training/education and feedback for shared learning in the context of invasive surgical procedures. This work is vital to help inform the development of novel methods to optimize shared learning in surgical innovation through the integration of findings into an electronic platform for real-time reporting and sharing of outcomes related to surgical innovation.

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Data Availability

This review will not generate any new data. All extracted data and results of the analyses will be made available as supplementary material in the publication of the review results.

Authors' Contributions

JMB, SP, KNLA, and NB developed the idea for this study. CH and MK prepared the protocol, which was reviewed, discussed, and approved by the entire study team. CH, MK, NA, and JR established and formulated the methods for this review, with input from RM, SP, KNLA, and SP. SP will provide general oversight for this study. SP, NB, and JMB will take the lead in implementing the findings from this study.

Conflicts of Interest

JMB is a member of the Core Outcome Measures for Effectiveness Trials Initiative Management Group. All other authors declare no conflicts of interest.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews) checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v11i9e37544_app1.pdf]

Multimedia Appendix 2
Search strategy for database searches.
[PDF File (Adobe PDF File), 145 KB - resprot_v11i9e37544_app2.pdf]

Multimedia Appendix 3
Initial list of data items to extract from eligible articles.
[PDF File (Adobe PDF File), 127 KB - resprot_v11i9e37544_app3.pdf]

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Abbreviations

BRC: Biomedical Research Centre
IDEAL: Idea, Development, Exploration, Assessment, Long-term study
NIHR: National Institute for Health and Care Research
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: PRISMA extension for scoping reviews

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Protocol

Group Antenatal Care in Ghana: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: While group antenatal care (ANC) has been delivered and studied in high-income countries for over a decade, it has only recently been introduced as an alternative to individual care in sub-Saharan Africa. Although the experimental design of the studies from high-resource countries have been scientifically rigorous, findings cannot be generalized to low-resource countries with low literacy rates and high rates of maternal and newborn morbidity and mortality. The Group Antenatal Care Delivery Project (GRAND) is a collaboration between the University of Michigan in the United States and the Dodowa Health Research Centre in Ghana. GRAND is a 5-year, cluster randomized controlled trial (RCT). Our intervention—group ANC—consists of grouping women by similar gestational ages of pregnancy into small groups at the first ANC visit. They then meet with the same group and the same midwife at the recommended intervals for care.

Objective: This study aims to improve health literacy, increase birth preparedness and complication readiness, and optimize maternal and newborn outcomes among women attending ANC at seven rural health facilities in the Eastern Region of Ghana.

Methods: Quantitative data will be collected at four time points using a secure web application for data collection and a database management tool. Data will be analyzed on an intention-to-treat basis to test the differences between the two arms: women randomized to group-based ANC and women randomized to routine individual ANC. We will conduct a process evaluation concurrently to identify and document patient, provider, and system barriers and facilitators to program implementation.

Results: The study was funded in September 2018. Recruitment and enrollment of participants and data collection started in July 2019. In November 2021, we completed participant enrollment in the study (n=1761), and we completed data collection at the third trimester in May 2022 (n=1284). Data collection at the additional three time points is ongoing: 6 weeks postpartum, 6 months postpartum, and 1 year postpartum.

Conclusions: This study is significant and timely because it is among the first RCTs to be conducted to examine the effects of group ANC among low-literacy and nonliterate participants. Our findings have the potential to impact how clinical care is delivered to low-literacy populations, both globally and domestically, to improve maternal and newborn outcomes.

Trial Registration: ClinicalTrials.gov NCT04033003; https://clinicaltrials.gov/ct2/show/NCT04033003

International Registered Report Identifier (IRRID): DERR1-10.2196/40828

(JMIR Res Protoc 2022;11(9):e40828) doi:10.2196/40828

KEYWORDS

group care; antenatal care; group antenatal care; health literacy; maternal health literacy; Ghana; sub-Saharan Africa; care seeking; maternal outcomes; neonatal outcomes

Introduction

Background

In 2017, the maternal mortality ratio in Ghana was estimated to be 310 per 100,000 live births for the 7-year period prior to the Ghana Maternal Health Survey [1]. While 89% of women in Ghana surveyed had attended the minimum standard of four antenatal care (ANC) visits, 20% of women continued to give birth at home [1]. In contrast to the decline in infant and under-5 mortality, neonatal mortality has remained stagnant since 2007 [1].

ANC has the potential to play a pivotal role in ensuring positive pregnancy outcomes for both mothers and their newborns [2]. While ANC is widely available and attended by the majority of pregnant women in Ghana, the expected impact on birth outcomes is yet to be fully realized. Thus, it is vital to examine the way ANC is being delivered and to explore alternatives to the current model to enhance positive birth outcomes.

In addition to its clinical components, ANC is designed to teach pregnant women to recognize the danger signs that might warn them of complications that could affect either themselves or their babies, and to encourage prompt care seeking for such danger signs. ANC is also designed to promote a healthy lifestyle, to integrate positive health behaviors, and to develop a trusting relationship with a health care provider and the health system.

While group ANC has been delivered and studied in high-resource settings for over a decade, it has only recently been introduced as an alternative to individual care in sub-Saharan Africa. Two randomized controlled trials (RCTs) examining group ANC versus routine individual care conducted in the United States found that women assigned to group care had significantly better antenatal knowledge, had greater satisfaction with care, and were less likely to have a preterm birth than those in standard care. In addition, the trials showed more favorable birth, neonatal, and reproductive outcomes in the intervention groups [3,4]. Although the experimental design of the studies from high-resource countries are scientifically rigorous, findings cannot be generalized to low-resource countries with low literacy rates and high rates of maternal and newborn morbidity and mortality.

In sub-Saharan Africa, data from three pilot studies found ANC delivered in groups to be acceptable and feasible to both women and providers in Ghana, Senegal, Tanzania, and Malawi [5-7]. A two-country cluster RCT found a higher likelihood of birth in a health care facility for Nigerian women in group versus standard ANC and a higher frequency of ANC visits in both Kenya and Nigeria [8]. Finally, a large cluster RCT conducted in Rwanda to examine the impact of group ANC on gestational age at birth found no significant difference in gestational age between intervention and control groups.

This is a critical time during which to examine group ANC in order to promote healthy pregnancy and optimize maternal and newborn outcomes in low-resource settings [9]. This paper describes the design and evaluation plan for a cluster RCT that is powered to fill the knowledge gap in women's health literacy skills in order to increase self-care knowledge and care seeking during intrapartum and postpartum periods.

Description of the Model for Group Antenatal Care

The World Health Organization (WHO) Standards for Maternal and Neonatal Care [9] guided our iterative process with content experts from the United States, Ghanaian health care providers, pregnant women, and stakeholders to ensure local and cultural relevance. The group-based ANC model in this study was developed and tested for acceptability and feasibility by the corresponding author (JRL) and her Ghanaian team for the first time in a clinical setting in Ghana [5,10]. At the core of the model is a negotiation process acknowledging that some health messaging may be in conflict with cultural beliefs. The model allows participants to incorporate safe, feasible, and culturally acceptable health beliefs into self-care actions by being inclusive of traditional practices that are not harmful. As part of the model, participants and the facilitator "agree" on safe and acceptable actions within the context of the setting that are then practiced by the group.

At the initial ANC visit, women are placed into small groups of 10 to 14 women with pregnancies of similar gestational age. Standard complete histories and physical exams as well as lab tests are completed, with group visits starting at the second ANC visit. Prior to the start of each group, blood pressure and weight are measured and a urinalysis is performed by each woman with help from the midwife. Each woman then receives an individual assessment with the midwife to measure fundal height, listen to fetal heart tones, and answer any questions she prefers not to raise in the group. The midwife and women then sit in a circle facing one another for a 60- to 90-minute facilitated discussion. The model uses strategies such as storytelling, peer support, demonstration, and teach-back to enhance its effectiveness. Health literacy is incorporated as an integral part of clinical practice within the model, not as an add-on to care.

Evidence-based information is presented in a nonhierarchical, patient-centered, participatory way. Picture cards (Figure 1) are used to enhance communication and learning in the group setting. They provide a mechanism to help convey new concepts and ideas.

The picture cards encourage valuable group discussion and are an educational aid to stimulate thinking and reflection, dialogue, and learning among participants. Content is repeated multiple times in a variety of ways to enhance retention, including the following: (1) auditory (ie, listening to stories and signs of problems), (2) visual (ie, through the use of demonstration and picture cards), and (3) kinesthetic (ie, practicing actions and handling picture cards).

The Facilitator's Guide for Group Antenatal Care, developed by JRL, provides a step-by-step guide that details how to conduct each of the group ANC visits, become a facilitator, enhance adult learning, provide respectful maternity care, and monitor for program quality, performance, and fidelity.

Figure 1. Examples of picture cards.

Aims and Objectives

The Group Antenatal Care Delivery Project (GRAND) is designed to improve health literacy, increase birth preparedness and complication readiness, and optimize maternal and newborn outcomes among women attending group-based ANC at seven rural health facilities serving predominantly low-literacy and nonliterate pregnant women in the Eastern Region of Ghana. More specifically, GRAND is designed to achieve the following aims:

- Aim 1: to quantify differences in birth preparedness and complication readiness, including knowledge of danger signs and recommended action steps, between women randomized to group-based ANC and those randomized to routine individual ANC.
- Aim 2: to assess behavioral differences in care-seeking patterns (eg, facility birth rates, postnatal care, and postpartum care) between women randomized to group-based ANC and those randomized to routine individual ANC.
- Aim 3: to evaluate the clinical outcomes of mothers and their newborns (eg, decrease in maternal morbidities and perinatal and neonatal mortality) between women randomized to group-based ANC and those randomized to routine individual ANC immediately postpartum and up to 1 year following birth.

We hypothesize that pregnant women randomized into group-based ANC, as compared to women who received routine individual ANC, will exhibit increased health literacy through the following: (1) increased birth preparedness, including recognition of danger signs and knowledge of how to respond to such signs; (2) higher rates of care-seeking behaviors, including seeking care for problems identified during pregnancy, higher facility delivery rates, and increased attendance at postnatal and postpartum care; and (3) better clinical outcomes for themselves and their newborns.

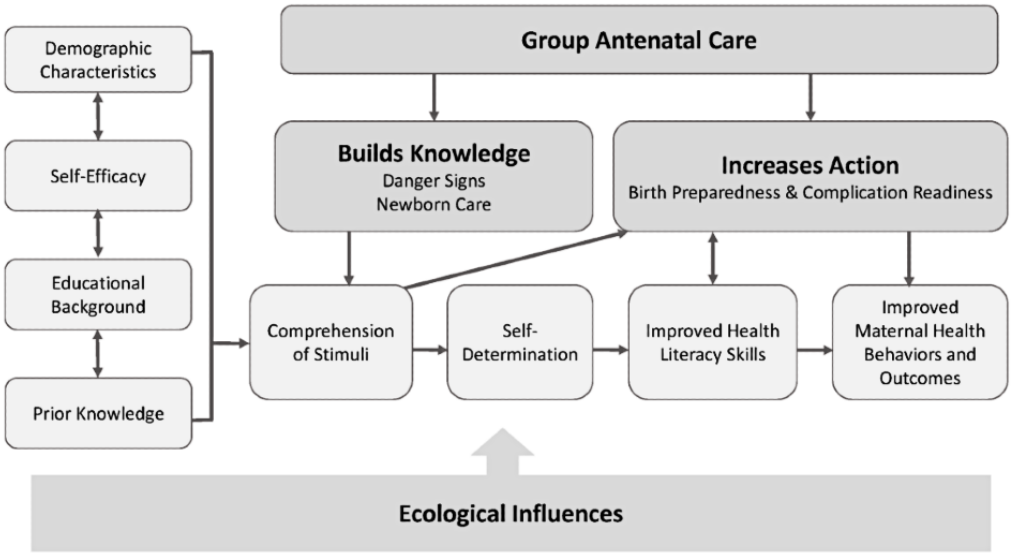
Methods

Overview

This study uses a theoretical model originally developed by Squiers et al [11] and modified in our preliminary research to assess maternal health literacy [5]. The Health Literacy Skills Framework uses an ecological perspective to help assist in the development and testing of potential interventions to impact a patient's health literacy [11]. As illustrated in Figure 2, our modified theoretical model, which is renamed the Maternal Health Literacy Skills Framework [5], is used to guide the aims and data analytic plan.

Our model addresses how group ANC builds knowledge by increasing the comprehension of stimuli, promoting self-determination, increasing action, and ultimately improving maternal health behaviors and outcomes. It considers how the individual's comprehension of stimuli and potential mediators may impact overall health behaviors and outcomes.

Figure 2. Modified Maternal Health Literacy Skills Framework.



Study Design

GRAND is a 5-year cluster RCT. The study was registered at ClinicalTrials.gov (NCT04033003) on July 25, 2019, and is a collaboration between the University of Michigan in the United States and the Dodowa Health Research Centre in Ghana. Health facilities were selected based the number of ANC registrants per month and the average gestational age of pregnancy among women at registration in each facility. Facilities were then matched based on facility type, district, and number of monthly ANC registrants.

Study Setting

The study setting for GRAND includes four districts—Akwapim North, Yilo Krobo, Nsawam-Adoagyiri, and Lower Manya Krobo—within the Eastern Region of Ghana. Ghana (Figure 3) has a population of approximately 30 million people and is situated in Western Africa between Togo, Burkina Faso, Ivory Coast, and the Atlantic Ocean.

Ghana is divided into 16 administrative regions, with the Eastern Region situated north and adjacent to the region that includes the capital city of Accra, the Greater Accra Region. While Greater Accra is predominantly urban and periurban, the Eastern Region relies on a primarily agrarian economy, including both subsistence and commercial farming. Approximately 20% of residents never attended any formal schooling, with another 60% stopping their education at the primary level (14.5%) or at the junior secondary (ie, high school) level (45.3%). Women are twice as likely as men to have never received any schooling [12]. According to the 2017 Ghana Maternal Health Survey, the fertility rate for the region is 3.8, comparable to the national average of 3.9 [1].

Figure 3. Map of study districts in Ghana.

Sampling and Randomization Frame

Facilities were randomized using a matched-pair method. Variables for matching included the number of deliveries and the average gestational age of pregnancy among women at the time of enrollment for ANC in each facility, so that facilities within each pair are similar to each other with regard to these matching factors. For each pair of facilities, one site was randomly assigned to group-based ANC (intervention) and the other to routine individual ANC (control). The matching and randomization process was completed using the nbpMatching package from R software (version 1.5.0; R Foundation for Statistical Computing) [13]. The locations of the chosen facilities ensures that participating facilities will be far enough apart to minimize the likelihood of cross-group contamination.

Power and Sample Size Calculations

We calculated the sample size based on three primary outcomes: the change in birth preparedness, complication readiness index scores, and the percent change in women obtaining maternal postpartum checkups and babies obtaining postnatal checkups within first 2 days after birth. See Table 1 for a complete list of primary and secondary outcomes.

According to the literature, the median intraclass correlation coefficient (ICC) was 0.010 [14]. Since we proposed a cluster randomized design based on seven intervention facilities and seven control facilities, we considered the effect of the ICC. The ICC is a measure of the extent to which the effect of the intervention differs across facilities. Hence, we conducted our sample size calculation for an ICC equal to 0.01 using the CRTSize package from R software [15]. First, the percentage of women in Ghana who were categorized as “prepared for birth” was 30% [16]. We expect that our ANC intervention will improve the preparedness to 45%, as measured by the birth preparedness and complication readiness index. At a significance level of .05, we need 84 women per facility to reach 80% power to detect such an effect. Next, approximately 60% of women in the Eastern Region of Ghana receive a maternal postpartum checkup in the first 2 days after birth [12]. We expect that our intervention will increase this value to 75%. To test this, we need 76 women per facility. Finally, the current percentage of newborns obtaining postnatal checkups in rural Ghana within 2 days is 22% [12]. We expect that our intervention will increase this value to 35%, in which case we will need at least 100 women per facility to see such an effect. To preserve power due to attrition, we proposed recruiting 120 women per facility. Hence, the total number of women to be recruited is 1680 based on an attrition rate of 20% in our pilot work.

Table 1. Primary and secondary outcomes.

Aims	Primary outcomes	Secondary outcomes
Aim 1: to quantify differences in birth preparedness, knowledge of pregnancy and newborn danger signs, and recommended action steps	• Ability to identify danger signs in pregnancy (eg, bleeding, severe headache, blurred vision, and fever) • Birth preparedness and complication readiness (eg, saved money, identified birth facility and emergency transportation to facility, and identified blood donor) • Ability to identify newborn danger signs (eg, poor suck, jaundice, difficulty or fast breathing, and convulsions)	• Ability to identify postpartum danger signs (eg, increased bleeding or large clots, weakness or fainting, fever, pain in abdomen or breasts, and painful urination) • Ability to identify the recommended action steps when a problem is identified (eg, call for help, have a plan for transportation, identify someone to accompany you to the facility, identify someone to care for the family, go straight to the facility, and supportive care along the way to the facility) • Self-efficacy, operationalized care-seeking history, and health information knowledge
Aim 2: to assess behavioral differences in care-seeking patterns (eg, facility birth rates, postnatal care, and postpartum care)	• Attendance at 4 or more ANC[a] visits • Facility birth • Four postnatal or postpartum checkups for both mother and newborn in the first 6 weeks after birth	• Uptake of modern family planning methods at 6 months postpartum • Infant immunized per EPI[b] scheduled at 1 year • Completion of IPTp2[c] malaria prophylaxis during pregnancy
Aim 3: to evaluate the clinical outcomes of mothers and their newborns (eg, decrease in maternal morbidities and perinatal and neonatal mortality)	• Maternal pregnancy-related morbidities (eg, puerperal sepsis and delayed postpartum hemorrhage) • Birth outcome (eg, stillbirth, live birth, and early neonatal mortality)	• At least 2 tetanus toxoid vaccines during ANC • Infant protected against neonatal tetanus • Hemoglobin level upon hospital admission, dichotomized as normal or anemic (<9.5 g/dL) • Infant birth weight (normal vs low [<2500 g]) • Repeat pregnancy within 1 year • Exclusive breastfeeding at 6 months

[a]ANC: antenatal care.

[b]EPI: Expanded Program on Immunization.

[c]IPTp2: intermittent preventive treatment of malaria for pregnant women.

Trainings

Training of Research Personnel

Prior to data collection, all research assistants (RAs) were trained for the study by the primary investigator and coinvestigators. All trainings were held in English, the official language of Ghana, with discussions regarding key terms in Dangbe, Ga, Akan, and Ewe. Trainings included the following: (1) an overview of the study and its protocol, (2) information about the ethical treatment of human subjects, (3) standardized record keeping and data collection for the study, and (4) strategies for reducing bias and error. Biannual refreshers will be conducted with all RAs. All RAs are fluent in English as well as in the dialect and culture of their assigned area.

Training of Clinical Personnel

Prior to data collection, we conducted a training of trainers for research personnel at the Dodowa Health Research Centre and maternal, newborn, and child health nurses representing the four District Health Directorates. All registered nurses and registered midwives providing ANC at both intervention and control facilities received an update on the essential components of ANC based on WHO guidelines to ensure equal quality at all sites at baseline. Providers at intervention sites were trained to implement group-based ANC, whereas providers at control sites will continue delivering routine individual ANC. Providers at study sites randomized to group care were trained in the delivery of the methodology. The provider training mirrors the facilitator's guide, including an emphasis on active listening, ideal conditions to maximize learning, and the use of picture cards as an important training resource for low-literacy learners. These trainers, with assistance from the primary investigator and two experienced trainers, then conducted a 3-day didactic training with groups of 10 to 12 clinical personnel focused on facilitating group ANC, use of the methodology, organizing groups, and an overview of the research. All trainings were in English, the official language of Ghana, with discussions regarding key terms in both English and the local languages. Participants then practiced delivering care using the group model with support from the trainers. A learning methods checklist and a fidelity checklist for provider readiness, which was established during preliminary studies, were used to provide feedback to participants during practice and to establish when each individual is ready to take on facilitating a group, based on the checklist scores.

Recruitment of Participants and Informed Consent

Recruitment of women will occur at individual health facilities. The trained RA works with clinic staff to identify women who meet the eligibility criteria and are healthy enough to discuss enrolling in an ANC intervention. The RA will inform health facility staff as to when they will be at the clinic and available to women interested in learning more about the study. Midwives will identify women (1) whose pregnancies are at less than 20 weeks' gestation; (2) who speak Dangme, Ga, Akan, Ewe, or English; (3) who are over the age of 15 years; and (4) who are not considered high risk.

The midwife will then instruct women who qualify to talk to the RA if they are interested in learning more about the study. Women who approach the RA will be read an approved recruitment script. Those who are willing to participate will be taken through an informed consent procedure and complete baseline data collection.

The procedure for informed consent includes the following:

1. An informed consent document in English is translated into Dangme, Ga, Akan, and Ewe.
2. The informed consent document is read aloud individually to all potential participants in private.
3. The Ghanaian RA asks the potential participant questions to ensure understanding of the research process and informed consent document and invites questions until the information is clear.
4. The participant signs the document or marks it with a thumbprint.
5. The RA uses the camera on the encrypted tablet to take a photograph of the signed or thumbprinted page; the image is then stored securely, similar to all study data.

In the Eastern Region, 10.4% of women and girls aged 15 to 49 years have never attended school, and only 15.7% have completed secondary school or higher [12]. A teach-back method will be used to confirm participant comprehension of the study requirements and methodology. The RA will ask potential participants to describe their understanding of the study's purpose, procedure, risks, and benefits using open-ended prompts and will repeat the material until understanding is achieved.

Data Collection and Measures

All quantitative data will be collected by trained RAs using encrypted and password-protected tablets as well as a secure web application for data collection and database management geared to support online and offline data capture for research studies. When an internet connection is not available, data will be collected offline and stored on the encrypted tablet. Once a connection is available, these data will be uploaded, verified for accuracy and completeness, and stored on a secure server.

No data will be collected by clinical providers. Data collection will occur at five time points in both intervention and control arms (see Table 2 for measurements at each time point):

1. Time point 0: the baseline session occurs immediately following the consent processes. Data are collected by trained RAs using a structured survey; health information is self-reported.
2. Time point 1: this session occurs at 34 weeks' gestation to 3 weeks postdelivery. Data are collected by trained RAs using a structured interview and by retrieving data from the ANC card.
3. Time point 2: this session occurs 6 to 12 weeks after delivery. Data are collected by trained RAs using a structured interview and by retrieving information from ANC cards on maternal and newborn clinical outcomes using a predetermined set of indicators.
4. Time point 3: this session occurs 5 to 8 months postpartum; data are collected via phone by trained RAs using a structured interview.
5. Time point 4: this session occurs 11 to 14 months postpartum; data are collected via phone by trained RAs using a structured interview.

During visits, midwives record clinical health–related outcomes (ie, place of birth, hemoglobin levels, newborn birth weight, maternal and newborn morbidities, stillbirth, and postpartum visit within 2 days postbirth) on the women's ANC cards. These data will be collected by the RA postdelivery.

Table 2. Measures and time points.

Time point and domains	Measure or source		
	Aim 1	Aim 2	Aim 3
Time point 0: enrollment			
1. Demographic characteristics	Baseline survey; section I: demographics	Baseline survey; section I: demographics	—[a]
2. Self-efficacy			
Extracting health information	Baseline survey; section II: self-efficacy	Baseline survey; section II: self-efficacy	—
Care-seeking history	Baseline survey; section II: self-efficacy and contraceptive self-efficacy scale	Baseline survey; section II: self-efficacy and contraceptive self-efficacy scale	—
3. Educational background			
Level of education	Baseline survey; section I: demographics	Baseline survey; section I: demographics	—
4. Prior knowledge			
Ability to identify danger signs, birth preparedness, and complication readiness	Baseline survey; section III: birth preparedness and complication readiness	Baseline survey; section III: birth preparedness and complication readiness	—
5. Health literacy skills	Maternal health literacy index	Maternal health literacy index	—
6. Ecological influences	Baseline survey; section I: demographics	Baseline survey; section I: demographics	—
Time point 1: third trimester			
7. Comprehension of stimuli	Third-trimester questionnaire	Third-trimester questionnaire	—
8. Self-determination			
Intent to use family planning and preparation for birth	Third-trimester questionnaire	Third-trimester questionnaire	—
Two or more tetanus toxoid vaccines and completion of IPTp2[b] malaria prophylaxis	ANC[c] card	ANC card	—
Time point 2: postbirth			
9. Clinical health–related outcomes	—	—	ANC card
10. Self-determination			
Attendance at 4 or more ANC visits	ANC card	ANC card	—
Adherence to care	Number of ANC visits	Number of ANC visits	—
11. Health-related behavior	—	—	Questionnaire for women who recently delivered, up to 6 weeks postpartum
12. Clinical health–related outcomes	—	—	Questionnaire for women who recently delivered, up to 6 weeks postpartum
Time point 3: 6 months postpartum			
13. Health-related behavior	Maternal health literacy index	Maternal health literacy index	6-month postpartum survey
14. Clinical health–related outcomes	—	—	6-month postpartum survey
Time point 4: 1 year postpartum			
15. Health-related behavior	—	—	1-year telephone survey
16. Clinical health–related outcomes	—	—	1-year telephone survey

[a]The data collected in the domain do not contribute to the research objectives of the aim.

[b]IPTp2: intermittent preventive treatment of malaria for pregnant women.

[c]ANC: antenatal care.

Process Evaluation

Overview

We will concurrently conduct a process evaluation to identify and document patient, provider, and system barriers and facilitators to program implementation. Using both quantitative and qualitative methods, we will identify potential and actual influences on the quality and conduct of the program's operations, implementation, and service delivery. We will employ structured observations of group sessions, interviews with providers, focus groups with women, and tracking logs to record how the intervention is delivered and received, document program fidelity, and identify opportunities to enhance the delivery of the intervention, while maximizing consistency in intervention delivery across sites. This process evaluation will add value to the analysis of the group ANC intervention by identifying barriers and facilitators at multiple levels throughout the study. For this process evaluation, we will focus on both fidelity of the intervention and dose, or frequency.

Individual Interviews With Midwives

All midwives involved in the intervention arm will be asked to participate in the process evaluation. Midwives will be approached by a member of the research team at the end of the seventh group meeting and asked if they are interested in providing feedback about group care. Those willing to participate will be taken through a consent process before the first interview begins. Each midwife will be interviewed at two random times, and each interview will last approximately 40 minutes. A structured interview using open-ended questions will be conducted to explore the midwife's perceptions of group versus standard ANC, barriers to implementation, challenges to integrating group-based ANC into the existing clinic workflow, and strategies that have helped with implementation. Interviews will be audiotaped, with permission from the participant, to ensure accuracy of responses; midwives can refuse to be audiotaped yet continue with the interview. The RA will write short-answer responses on a data collection form. Audiotapes will be transcribed and deidentified; tapes will be destroyed immediately after transcription. We have seven health facilities randomized to the intervention arm and 2 to 4 midwives at each facility; as each midwife may be interviewed twice, we expect that approximately 56 midwives may participate in the process evaluation.

Focus Group Discussion With Participants

Groups of women in the intervention arm will be randomly selected to participate in focus groups for process evaluation. We anticipate 10 random groups of 10 women through the course of the study for a total of 100 women in the focus groups. Women will be asked to describe their perceptions of group versus standard ANC, their perceptions of the value of group ANC, and how they could envision the process being improved.

Focus group discussions will be led by a member of the research team with randomly selected groups of women completing group ANC throughout the study. Focus groups participants will provide consent individually before they enter the focus group room so they may choose whether they want to participate. The group will be conducted in a private setting, and names will not be used during the discussion. Audiotapes will be transcribed and deidentified; tapes will be destroyed immediately after transcription. Each focus group discussion will last about 1 hour.

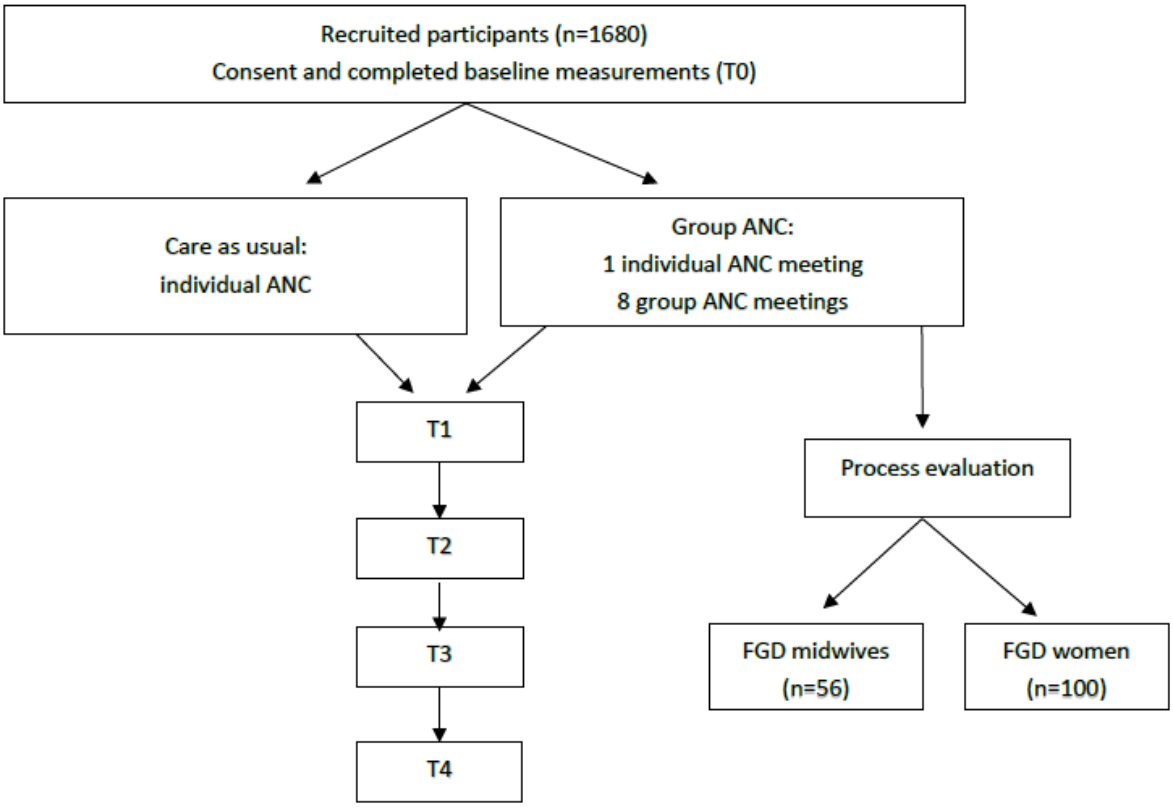
Structured Observations

A sample of 2 out of 7 group ANC visits will be observed for each provider to monitor fidelity to the model (eg, whether content is delivered as intended, women are engaged enough to actively participate in group discussions and activities, picture cards are used as written in the facilitator's guide, and feedback is provided to participants during demonstrations).

Tracking Logs

A brief form will be completed by the midwife provider each time an ANC visit is held to track the date of the session and the number of participants from the group in attendance, in order to track dose. See Figure 4 for flow diagram of enrollment and data collection.

Figure 4. Flow diagram of enrollment and data collection. ANC: antenatal care; FGD: focus group discussion; T0: time point 0 (baseline); T1: time point 1 (34 weeks' gestation to 3 weeks postdelivery); T2: time point 2 (6-12 weeks after delivery); T3: time point 3 (5-8 months postpartum); T4: time point 4 (11-14 months postpartum).



Data Analysis: Aims 1 to 3

Data from all participants randomly assigned to the intervention or control groups will be analyzed on an intention-to-treat basis. Deviations from randomized allocation will be reported. We will also conduct per-protocol analysis by eliminating noncompliers in the analysis. Summary statistics based on mean, SD, or frequency will be used to characterize the sample distribution of each arm. Proper transformations will be investigated and taken if the sample distributions of continuous variables violate the normality assumption. For aims 1 to 3, generalized linear mixed models will be used to test the differences between the two arms since a cluster RCT design will be used. There are four components in generalized linear mixed models: outcome variable, fixed effects, random effect, and link function. The fixed effects include an explanatory variable and covariates. In this study, all three aims have the same explanatory variable, which is a binary variable indicating the arm to which women are assigned. The study sites, gestational age, and women's demographic variables, such as education or literacy, marital status, pregnancy history, and medical history, will be added to the generalized linear mixed models as covariates to increase the precision of the estimates. The random effect is comprised of the 14 facilities. In this study, a random intercept model will be used to account for the cluster effect. The outcome variables and link functions in generalized linear mixed models depend on the aims and are described below. The construct of the generalized linear mixed models is to test whether the explanatory variable is significant at the level of .05 using the likelihood ratio test.

For aim 1, to quantify differences in the recognition of pregnancy and newborn danger signs and knowledge of recommended action steps, the birth preparedness and complication readiness index will be measured at enrollment and at the third trimester. We will add baseline data as covariates. The logit link function will be used for each binary birth preparedness and complication readiness question to test the efficacy of the group-based ANC method. The identity link function will be used when the outcome variable is a summary statistic of the birth preparedness and complication readiness index. When the *P* value of the explanatory variable is less than .05, we will declare a significant difference between the two arms. Average changes in birth preparedness and complication readiness summary statistics or odds ratios for each question will be used to quantify the effect of the group-based ANC intervention.

For aim 2, where we will assess behavioral differences in care-seeking patterns between the two arms, the outcome variables are frequency of attendance of ANC visits, facility birth, and postnatal or postpartum care. For the attendance outcome variable, the identity function will be used. For facility birth and postnatal or postpartum care, the logit link function will be used. When the *P* value of the explanatory variable is less than .05, we will declare a significant difference between the two arms. The effect of group-based ANC on attendance will be quantified by the average difference. The effects of group-based ANC on facility birth and postnatal or postpartum care will be quantified by odds ratios. For the secondary outcomes in aim 2, the logit or identity link function will be used in a way similar to the primary outcomes.

For aim 3, in order to evaluate the clinical outcomes of mothers and their newborns, the outcome variables are maternal pregnancy-related morbidities and newborn birth status. For maternal morbidities, the logit link function will be used. Since newborn birth status is classified into three categories—stillbirth, live birth, and early neonatal mortality—the cumulative logit link function [17] will be used. When the explanatory variable is significant at .05, the effect of group-based ANC on maternal pregnancy-related morbidities and newborn birth status will be interpreted using the odds ratio. We will illustrate the difference between outcomes using odds ratios for each pair of newborn birth statuses. The secondary outcomes will be analyzed similarly using identity or logit link functions.

For multiple outcomes in the same family, we will conduct direct inference using the Holm multiple testing procedure [18] to control for the family-wise error rate at a level of .05 [19]. The generalized linear mixed model analysis will be carried out using the lme4 package from R software [20]. All findings will be reported using the CONSORT (Consolidated Standards of Reporting Trials) statement as a guide [21]. Full transparency will be provided when reporting experimental details so that others may reproduce and extend our findings.

Data Analysis: Process Evaluation

The approach by Steckler et al [22] will guide the analysis of our process evaluation of the data. Qualitative data will be obtained from semistructured interviews. All qualitative data will be collected by the research team and will be transcribed verbatim into English, leaving key phrases that are difficult to translate intact, with the closest approximate meaning put into parentheses in the transcript. No data will be collected by clinical providers. All transcripts will be stored on a password-protected server. All data from semistructured interviews will be entered into NVivo qualitative software (QSR International) to assist with the identification of key themes. Structured observations will be recorded and summarized for key points. The use of an audit trail composed of methodological and analytical documentation and validation with colleagues will be used to achieve validity.

Ethics Approval

This study and all procedures were approved by the Institutional Review Boards (IRBs) at the University of Michigan (HUM-00161464) and the Ghana Health Service (GHS-ERC016/04/19). This is a report of a study protocol; therefore, human subject consent was not necessary. As required by the University of Michigan, regardless of the country of residence, all research staff, including principal investigators, coinvestigators, and RAs, on research projects that involve human study participants must complete the online program for education and evaluation in responsible research and scholarship or equivalent, and they must have their human subjects certification renewed every 3 years.

Results

The study was funded in September 2018. During the first year, we completed the following:

1. Developed a detailed research protocol.
2. Submitted the research protocol for full board approval to the University of Michigan, the Dodowa Health Research Centre, and the Ghana Health Service.
3. Received IRB approval with contingencies.
4. Updated the facilitator's guide and training materials for providers to reflect the new WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience [9].
5. Hired and trained 6 Ghanaian RAs in the ethical conduct of research, the data collection protocol, and the use of research electronic data capture (REDCap) [23,24] for secure data management.
6. Developed and pilot-tested data collection instruments with modifications for the local context.
7. Identified study sites for inclusion.
8. Randomized study sites.

Study data are collected and managed using REDCap at the Dodowa Health Research Centre. REDCap is a secure, web-based software platform designed to support data capture for research studies. REDCap provides (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources [23,24].

We also conducted a 3-day training for 10 champion trainers: 2 from each district in the research study and 2 from the provincial headquarters. The training covered an introduction to the study, an update or refresher on Ghanaian guidelines for ANC, and how to conduct group ANC using the facilitator's guide and methodology. A learning methods checklist was employed to ensure fidelity to the model. A schedule was prepared for the next 2 weeks of training at the district levels.

Recruitment and enrollment of participants and data collection started in July 2019. In November 2021, we completed participant enrollment in the study (n=1761), and we completed data collection at the third trimester in May 2022 (n=1284). Data collection at the additional three time points is ongoing: 6 weeks postpartum, 6 months postpartum, and 1 year postpartum. We are currently conducting preliminary data analysis and expect the results to be published in 2023.

Discussion

Overview

We hypothesize that pregnant women randomized into group-based ANC will exhibit increased birth preparedness and complication readiness, including recognition of danger signs and knowledge of how to respond to such signs. This may result in higher rates of care-seeking behaviors, including seeking care for problems identified during pregnancy, higher facility-based delivery rates, and increased attendance at postnatal and postpartum care appointments.

This study is significant and timely because it is the first cluster RCT to be conducted in Ghana to examine the effects of group-based ANC on maternal and newborn clinical and behavioral outcomes. Ghana is one of 24 priority countries targeted by the United States Agency for International

Development to improve maternal and child health and end preventable death [25].

Recent recommendations by the WHO call for rigorous research into group ANC to improve the use and quality of care [9]. A strength of our study is the use of a theoretical framework to examine health literacy. Initially considered as a patient's ability to read and understand written information, health literacy is now more broadly defined as a person's ability to acquire or access information, understand it, and use the information in ways that promote and maintain good health [26,27]. Despite a burgeoning emphasis on health literacy in high-resource countries [28], there are a dearth of studies examining interventions to improve health literacy in low-resource settings [29]. Even fewer studies have examined maternal health literacy, defined as the "cognitive and social skills which determine the motivation and ability of women to gain access to, understand, and use information in ways that promote and maintain their health and that of their children" [29]. New approaches to improve health literacy are sorely needed in countries where women and newborns continue to die from preventable causes [30].

Our process evaluation will allow us to contribute to a growing body of evidence that identifies barriers and facilitators to the implementation of group ANC. Findings from the process evaluation will contribute to eventual scale-up of the intervention in Ghana should group ANC be shown to improve maternal and newborn outcomes.

Our research team is committed to disseminating the findings from this proposed study in four different ways: (1) presentations at national and international conferences; (2) journal articles in peer-reviewed journals, including open access for our international colleagues; (3) community presentations, media events, and other public venues where we intend to discuss our findings; and (4) meetings and presentations with the Ghana Health Service to discuss cost-effective ways for scaling up the project and ensuring sustainability.

Limitations

Although we have designed a rigorous cluster RCT, neither the study sites nor the participants are blinded to the study conditions because providers at sites have been trained to deliver group ANC. We eliminated selection bias by randomly selecting sites using a stratified random sampling method from the sampling package in R software. Participating sites are limited to one rural area of Ghana; thus, results may not be generalizable to urban settings. However, results could guide country-wide policies for improving maternal and newborn health, and results could highlight the benefits of group ANC for similar rural areas across Africa where maternal and newborn morbidity and mortality are high.

Improving maternal and newborn health outcomes has been a major focus for the governments of many low- and middle-income countries, including Ghana. Free maternal and child health has been introduced in Ghana as part of a comprehensive policy to improve maternal health care delivery and reduce maternal and child deaths [1]. Group ANC has the potential to improve the quality of care and pregnancy outcomes for women and their newborns. Findings from this study will provide strong evidence and lessons learned to contribute to future policies and scale-up for all of Ghana.

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Data Availability

We will comply with all National Institutes of Health (NIH) policies on data sharing. Full transparency in reporting experimental details will be given so that others may reproduce and extend our findings. Deidentified data will be shared in Deep Blue for those wishing to conduct a secondary analysis of the data. Deep Blue is the University of Michigan's permanent, safe, and accessible service for providing access to the work conducted by researchers at the University of Michigan. The repository has data access policies and procedures consistent with NIH data sharing policies. Submitted data will conform to relevant data standards. Data will be deposited within 1 year of completion of the funded project period for the award or upon acceptance of the results for publication. We will identify where the data will be available and how to access the data in any publications and presentations authored or coauthored regarding these data, as well as acknowledge the repository and funding source in any publications and presentations.

Authors' Contributions

JRL, JEOW, and CAM were involved in all aspects of conceptualization and study design. JRL, CAM, and NL wrote the initial draft of the Group Antenatal Care Deliver Project protocol that was submitted for ethical review, with input from JEOW, VAK, VEAA, EAA, RZ, and KHJ. All authors contributed to the development of the protocol and manuscript and reviewed and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

ANC: antenatal care
CONSORT: Consolidated Standards of Reporting Trials
GRAND: Group Antenatal Care Delivery Project
ICC: intraclass correlation coefficient
IRB: Institutional Review Board
NIH: National Institutes of Health
RA: research assistant
RCT: randomized controlled trial
REDCap: research electronic data capture
WHO: World Health Organization

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